1951

Neurology

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

VOLUME II

JANUARY 1952 – DECEMBER 1952

LANCET PUBLICATIONS, INCORPORATED
Minneapolis, Minnesota

Neurology

OFFICIAL JOURNAL
OF THE
AMERICAN ACADEMY
OF
NEUROLOGY

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Neurology

The Syndrome of Periodic Paralysis

William W. Hofmann, M.D.

CLASSICALLY described, periodic paralysis is a hereditary disease which begins during the second decade of life and is characterized by recurrent attacks of flaccid paralysis associated with low levels of serum potassium. The case reported here is added to the literature because it presents some unusual features both clinically and with reference to laboratory data. It will be shown that the findings in this case represent merely the "final common pathway" for a wide-spread metabolic disorder, and that periodic paralysis should be considered a symptom-complex rather than a clearly defined disease entity.

HISTORICAL REVIEW

Concepts of periodic paralysis have changed considerably since the term was first applied in 1853 by Cavare.[1] Early writers on the subject noted many common features in their reports. As the literature grew, however, more and more contradictory observations were recorded, and cases began to appear in which the same signs were found associated with other diseases. Charcot[2] was probably the first to report the occurrence of paraparesis and paraplegia in conjunction with thyrotoxicosis. In the same period Rosenfeld[3] noted paroxysmal acute ascending paralysis of the so-called "Landry's" type in Basedow's disease, and MacKenzie remarked on paralytic phenomena in the lower extremities of certain patients with thyroid disease.[4] Before the turn of the century, Mitchell[5] and others recorded transient recurring paralyses which seemed to run in families, even though there was no evidence of an endocrine disorder.

From the division of neurology, University of Minnesota Medical School, Minneapolis, Minnesota.

Kitamura[6] again noted the relationship between thyrotoxicosis and periodic paralysis in 1913, and by 1925 Shinosaki[7] had collected at least 15 sporadic cases with exophthalmic goiter and periodic paralysis. Thus it became evident that there was a sporadic type of recurrent paralysis associated with thyroid disorders and another type occurring in several members of certain families. Later, additional cases were described which were not familial or related to another systemic disease. It has also been shown that the syndrome can be produced by various artificial means, and more recently it has occurred during certain types of therapy as a side-effect of the medication. Attacks of paralysis may be induced in susceptible persons by such agents as physostigmine, pilocarpine, parathormone, pituitrin and acetylcholine.[8] Otherwise normal persons may be almost paralyzed by the continued use of hormones which have a marked effect on body electrolytes. Thus ACTH, testosterone, insulin and desoxycorticosterone acetate have been implicated in some types of transient paralysis.[8, 9, 10] Nonendocrine disorders such as congenital intestinal alkalosis,[11] sprue, acute diarrhea and even malaria have been shown to be responsible for other cases of recurrent paralysis.[8, 12]

In 1901 Singer and Goodbody[13] discovered that potassium administered by mouth to patients with the classical paralysis was both a cure for the acute attack and a means of preventing further episodes. In 1937 Aitken et al.[14] found that the serum potassium was definitely lowered during these attacks. Since that time, extensive studies have been carried out in almost all bodily functions influencing mineral, food and hormone metabolism in these cases. Results have shown that what helps one case may harm another, and what induced an attack in one may have no apparent effect in a similar clinical case. Also, there has been no uniformity of results, not only in different patients, but occasionally in the same patient during different attacks. Thus it appears that the syndrome briefly described in most texts as periodic paralysis can be produced in many different ways and that its primary physiopathology is probably not as simple as was supposed previously.

CASE HISTORY

A 31 year old white male electrician was sent to the hospital with a tentative diagnosis of severe bulbar poliomyelitis. His chief complaint was that of progressive weakness of four days' duration. Except for mild diarrhea, he had been well until four days prior to admission, when he noticed some pain and stiffness in his thighs on arising in the morning. There was some mild difficulty in ascending the stairs, but this disappeared shortly afterwards. On arising the next morning he again noted weakness in his legs as well as a mild generalized weakness, but he was able to work that day. The same sequence was repeated on the third day. On the day of hospitalization the patient

awoke early in the morning and felt much worse. He went to the bathroom and then found he was unable to rise from the toilet. He stated that he was extremely weak in all four extremities and had to be lifted back to bed. He had no difficulty in swallowing, but there was some weakness of respiration. There was no history of fever, upper respiratory infection, sore throat, stiff neck or headache. He had never been exposed to any toxins, such as gasoline, lead, other heavy metals or poisonous organic compounds.

Past history revealed that the patient had had diarrhea for nine months preceding hospitalization. There was no associated nausea, vomiting, abdominal pain or weakness, and the patient had been working steadily. No melena, tarry stool or excessive mucus discharge were noted, and the stools were not foamy or especially foul. The patient had suffered mild bowel disturbances while overseas with the army, and several men in his company were diagnosed as having amebic dysentery. However, repeated stool cultures and examinations by his physician showed no infection to account for his present symptoms. He had worked in a tuberculosis sanatorium, but guinea pig innoculation revealed no evidence of tuberculous enteritis. Though the patient was rather concerned about the diarrhea, further questioning revealed that he had had at most five or six stools per day, and these were always well formed. The rest of the past history was essentially noncontributory, except for the fact that the patient had been given a medical discharge from the army because of rather severe migraine headaches. These had not been especially troublesome during the present illness.

System review was negative, but family history revealed that the patient's sister had entered the hospital about one year previously because of weakness. This was, however, associated with fever and stiff neck. Lumbar puncture revealed only one lymphocyte, and she was discharged because of the lack of findings. The fever she had on entry was attributed to an inflamed and infected pharynx. No other relatives have ever had any weakness or paralysis. An uncle and the patient's mother both had enlarged thyroid glands.

On physical examination the patient appeared acutely ill. He was perspiring heavily, the pupils were widely dilated, and respirations were short and shallow because of intercostal muscle weakness. There was no fever, but the pulse was rapid and the initial blood pressure was 165/0-10. The right lobe of the thyroid was diffusely enlarged and rather soft. There was no bruit. Inspection of the heart area showed a heaving precordium and apex, but there was no thrill. The heart seemed enlarged to percussion, and ausculation revealed a grade one mitral systolic murmur with an irregularity consisting of trigemini.

Neurologic examination showed the most significant findings. The patient was alert, oriented and cooperative, though somewhat apprehensive. He could not lift his head from the bed, nor could he turn about unassisted. There was flaccid paralysis of the legs, but he could move his arms a little. Intercostal and trunk muscles were involved to a lesser extent. Though the pupils were dilated, they reacted well to light and accommodation. There was very slight weakness of palatine, pharyngeal and sternocleidomastoid muscles, but no stiffness of the neck and no muscle spasm. Though the neuromuscular involvement was diffuse, initial examination showed the reflexes to be diminished in a rather patchy fashion. Complete areflexia and flaccidity developed after about one hour in the hospital. At no time were any of the pathologic reflexes present. Sphincters were intact.

Initial laboratory studies showed nothing remarkable except a low serum potassium level, and it was decided that the patient was suffering from his first attack of periodic

TABLE 1

TABULATION OF LABORATORY FINDINGS ON FIRST HOSPITAL ENTRY

Date	7/12	7/12	7/13	7/14	7/15	7/16	7/17	7/18	7/19
Blood									
Potassium	2.1	2.2	2.2	4.8	5.1		5.2		5.2
Sodium	149		159	141			143		139
CO_2 combining power	14		20	26			24		
Protein			5.6			6.7			
Albumin			3.1						
Globulin			2.5						
Hgb	14.7			16.2					
RBC	4.9m			5.5					
WBC	10,500			10,360					
pmn	73			64					
lymph	17			27					
mono	9			9					
Chlorides	117		100	109					106
Sed. rate (1 hour)	5.5m								
Urine									
Albumin	Tr.					Neg.			Neg.
Sugar	Neg.					Neg.			Neg.
WBC	Neg.					Neg.			Neg.
RBC	Neg.					Neg.			Neg.
Coproporphyrins (24 hour)	Expressed as Gamma		688				857	857	
Spinal Fluid									
WBC	Neg.								
RBC	Neg.								
Protein	21								
Chlorides	128								
Serology	Neg.								

NOTE: Low initial value of potassium and relatively slow rise on 7/12 and 7/13 despite steady administration of potassium. Note also high urinary coproporphrins (not fractionated).

paralysis. Accordingly, treatment with potassium chloride was instituted. The patient was unable to retain the solution by mouth, and an intravenous infusion was given. Though the actual serum level of potassium did not rise appreciably from the original value, the patient showed definite response after the administration of 6 gm. of potassium chloride. Thereafter he was maintained on potassium citrate by mouth, and recovery was gradual but complete. The initially high values for serum sodium returned to normal as potassium was given. This may be interpreted as an example of the inverse ratio between sodium and potassium which has been seen in other conditions.[23] After further laboratory studies, which are summarized in table 1, the patient was discharged to return to work.

Approximately one month later the patient suffered a brief period of weakness while working. He was readmitted to the hospital for definitive metabolic studies and therapy, although he was in no distress at this time and serum potassium was normal. However, he showed further weight loss, and there was some asymmetry of reflexes. The biceps and knee reflexes were definitely depressed when compared to the others,

but there was no atrophy or fasciculation. Since the metabolic rate was still elevated, it was considered possible that the patient had developed myopathy secondary to endocrine disturbance. A biopsy of the right deltoid muscle showed essentially normal tissue.

In order to evaluate the relationship between the patient's thyroid disease and his neuromuscular disorder, it was felt that an attack of paralysis should be induced and different methods of treatment should be tried. Accordingly, several attempts to cause paralysis were made with agents which are known to produce attacks in most susceptible persons. Three hundred grams of glucose by mouth, 100 gm. by vein, 20 units of insulin alone, and 40 units with 100 gm. of glucose, as well as adrenaline injections were all used without any measurable effect except slight and transient weakness. It was also found that these agents were not effective in reducing the level of serum potassium to a significant extent. Though the patient had previously entered the hospital with classical paralysis, thyrotoxicosis and low potassium, it now appears that he was in some way protected against electrolyte shifts even though conditions were the same externally. After repeated failures to lower the potassium level and cause paralysis, it was decided that the patient should be observed further and that his metabolic disease should be treated. Laboratory studies done before he was discharged are shown in table 2.

TABLE 2

	A	B	C	D
Potassium	5.8 M. eq./L	5.5	5.0	4.9
Phosphorus	4.5 mg. %	3.9	3.9	4.4
Glucose	88 mg. %	—	—	—
Calcium	11.4 mg %	10.9	—	12.2
Sodium	137 M. eq./L	143	—	—

A—On Admission
B—After oral administration of 300 gm. of glucose
C—Twenty minutes later—after administration of 10 units of insulin
D—One hour—after 10 additional units regular insulin and 0.5 ml. 1/1000 adrenaline

Examinations of the urine, blood count, differential and stool were all within normal limits. Twenty-four hour urinary coproporphyrin levels were 1268 gamma and 1578 gamma on two different days. Tracer doses of radioactive iodine showed 57 per cent uptake over the thyroid region, and 87.5 per cent was protein-bound iodine. Basal metabolic rate was plus 57 per cent shortly after first entry and plus 47 per cent during the second hospital stay. Agglutinations for typhoid, paratyphoid and brucellosis were negative.

After the preliminary workup had been completed, this man was discharged to the out-patient department on a course of prophylthiouracil. Potassium therapy was omitted with the consideration that, should hyperactivity of the thyroid be in some way protecting against periodic paralysis in this case, decreasing the activity of the gland might cause the attacks to recur. In such a case a clearer explanation of recurrent paralysis in some patients might be obtained.

Discussion

Classification of Periodic Paralysis: For sake of clarity it might be

well to classify this syndrome with reference to its possible causes. As stated earlier, the descriptions of this disease have of necessity become more and more inclusive as new and different manifestations have been reported. It seems that the term must include the following groups and that the words paralysis or paresis be used interchangeably. The clinical picture in these groups may be identical even though the primary etiology is different.

1. "Classical" type—with definite family history
   a. Those with no apparent associated systemic disease
   b. Those with associated systemic disease
2. Periodic paralysis in isolated cases—no family history
   a. With associated systemic disease
   b. Without associated systemic disease
3. Recurrent paralysis arising after primary systemic disorder
   a. Chronic thyrotoxicosis
   b. Hyperinsulinism
   c. Hypercorticoadrenalism
4. Recurrent paralysis after medication
   a. Desoxycorticosterone acetate—as used in Addison's disease
   b. ACTH
   c. Testosterone
   d. Insulin
   e. Phenobarbital and assorted drugs used by other observers

Whether there is overlapping among some of these cases cannot be stated until more exact methods are available for the diagnosis of general metabolic disorders. It appears that the patient under discussion probably best belongs in group 2a, but this was not discovered immediately. It was felt at first that the whole picture could be explained on the basis of the very low serum potassium level. It is known that many patients with periodic paralysis also have a palpable thyroid without showing obvious signs of hyperactivity of the gland,[15] and this finding was not given very much consideration in the preliminary examination. It is also established that in some cases there is a rather profound anxiety reaction to the paralysis,[16] and perspiration, tachycardia and wide pulse pressure are relatively common findings in these patients.[17] Though some observers have reported high systolic and low diastolic pressures during a seizure,[18] one might have suspected something besides hypokalemia in this case, since other reports have not shown such a "wide open" circulatory system. The family history of goiter in an uncle and the patient's mother might also have led one to look for an endocrine disturbance here. It has been noted that there is a rather high incidence of goiter in families of patients with periodic paralysis.[8] In this case, laboratory studies done after the initial examination showed that the patient was afflicted with two diseases.

Clinical Description of the Disease: The actual attack of paralysis

in this patient was similar in most respects to those described in the literature, and it was not a partial or "mild" seizure such as some experience, nor was it the insidiously developing weakness seen after the use of some of the drugs and hormones mentioned above. The rather patchy decrease in the deep tendon reflexes on first examination has been observed in other patients. As is usually the case, this patient progressed to complete areflexia in the involved areas. The persistence of some reflex changes during the interval period may herald the development of organic muscle disease secondary to thyrotoxicosis, though this was not evident in the one specimen obtained. Involvement first of the lower extremities is typical of periodic paralysis,[8] and this man complained first of stiffness of the legs. It is interesting that patients with long-standing thyrotoxicosis often complain of a similar weakness of thigh muscles. The cardiac arrythmia in this patient was interpreted as trigemini on clinical examination, and the first electrocardiogram taken showed this to be the case. Various types of cardiac involvement have been recorded by other writers, and transient arrythmia, cardiomegaly and systolic murmurs are common.[8] Gass et al.[19] reported a case with bigemini in 1948. A Wenckebach phenomenon was shown on the tracings in the patient under discussion, and it is interesting that prolonged A-V conduction time has been found previously in association with low serum potassium levels.[20] This same sort of conductive defect has been observed with digitalis, and it has been said that the glycoside may exhibit this effect by lowering the intracellular concentration of potassium in the myocardium.[19]

Most observers have noted no constant relationship between bowel activity and the development of paralytic seizures, but Crafts[21] reported a case in 1900 where attacks were accompanied by diarrhea. It is known that patients with hyperthyroidism may show mild overactivity of the bowel, just as their functions are speeded up generally,[22] and severe acute or chronic diarrhea may cause marked weakness due to loss of potassium.[11] It is certainly doubtful whether the mild diarrhea noted by this patient could have been responsible for the very low potassium he showed on entry.

Many patients with periodic paralysis find that a high carbohydrate diet favors the development of attacks,[11, 7] and some investigators have found that parenteral administration of glucose will precipitate paralysis.[7, 19, 8] The patient presented here had been on just such a diet prescribed by his local physician in an attempt to alleviate the bowel symptoms. McQuarrie[11] has found that a carbohydrate-to-potassium ratio below 65 helps to prevent attacks, as does fasting and a high protein diet.

Even in the most severe attacks these patients are characteristically alert and oriented.[5, 12, 23] It is rare to find as much cranial nerve involvement as was shown in this case, but there have been reports of aphasia with a seizure,[24] paralysis of muscles of deglutition and respiration in a fatal case,[25] and ptosis with blurring of vision in still another case.[13] Ordinarily there is no detectable abnormality of sensation, and there was none found in this case. If, as some workers have theorized,[26, 27] this condition is a disorder of the central nervous system, it appears to involve only the motor components.

There are no constant changes in the formed elements of the blood, but in this case there was a mild lymphocytosis on one occasion. In 1898 Taylor[28] described a transient elevation of the white cell count with lymphocytosis during attacks, but this has not been borne out by other observers, and it is possible that this change was secondary to a mild degree of hyperthyroidism which was not recognized at the time. Frequent examinations of the urine have shown no significant abnormality as a rule, but Shinosaki[7] observed transient acetonuria and glycosuria. The spinal fluid chemistry is within normal limits,[19] and the serological tests for syphilis are negative.

The basal metabolic rate was significantly elevated during the patient's recovery period, and this finding in conjunction with the increased uptake of radioactive iodine and high protein-bound iodine confirms a clinical diagnosis of thyrotoxicosis. The question arises whether his neuromuscular dysfunction may have played a part in raising the metabolic rate or whether the thyrotoxicosis per se led to a decrease in serum potassium and paralysis. The literature contains reports of marked elevations of metabolic rate during attacks in some patients[29, 30] and significant drops in others.[30] It is doubtful that flaccid paralysis in itself would cause an increased oxygen uptake, and the relationship of the thyroid to potassium is discussed later.

An association between periodic paralysis and migraine has been a fairly common finding,[31] and the history of such headaches in this patient is therefore important. In one series of cases the agent used to combat the paralysis also helped the headaches.[30]

The laboratory findings on the first entry agree with those of other workers, and an attempt will be made to correlate them with some of the more recent theories in regard to the pathogenesis of this disease.

Pathogenesis: An impressive amount of detailed investigation has been done to explain the fundamental changes responsible for the paralyses and pareses seen in these patients, but most of the data are so contradictory that specific conclusions are impossible. It is not the purpose

of this paper to present any new concepts; instead, a brief review of the literature is presented.

A deficit in serum potassium can no longer be considered the *sine non qua* in periodic paralysis, even in the classical familial type.[30] Nor should it be expected that all cases will respond satisfactorily to such a simple remedy as potassium salts.[32] It should be remembered that the disease is not entirely benign, for several fatalities have been reported,[7, 25, 31] and occasional long-standing cases have been found to develop definite organic changes.[33]

Paralysis or paresis of muscles when there is a deficiency of potassium is understandable in the light of several classical experiments by Feldberg,[34] Vartiainen,[35] Brown[36] and Bronk.[37] The role played by potassium in synaptic transmission was shown by injections of potassium chloride into the fluid perfusing the superior cervical ganglion. This resulted in stimulation of the nerve cells and liberation of acetylcholine. Curarine, which blocks transmission at synaptic junctions, does so by preventing acetylcholine from acting on the ganglion cell, but it seems to intensify the response to potassium. The output of acetylcholine from the preganglionic endings is not changed by curare. It has been suggested that potassium is not directly concerned in the propagation of an impulse across the synapse, but that the liberation of acetylcholine, which may be the actual chemical medicator, is dependent upon the mobilization of potassium ions by the preganglionic impulse. It has also been postulated from the work of these observers that the appearance of potassium ions at the synapse conditions the actions of acetylcholine upon the ganglion cell. Bronk and his co-workers[37] showed that calcium also plays an important part in the excitation mechanism. Apparently calcium is necessary in order that potassium act on the synapse. Since essentially the same chemical and electrical reactions take place at the peripheral neuromuscular junctions, these observations can be extended to help clarify the situation in those cases of periodic paralysis accompanied by low potassium levels. The marked response to potassium in such patients substantiates the theory that a deficiency of the ion at the neuromuscular junction is one of the most important factors in the development of paralysis. Also, failure of the muscles to react to electrical stimulation[5, 8] during the seizure points toward an ionic imbalance rather than interference with production or action of acetylcholine, since curare, which blocks response to the chemical mediator, still allows the muscle to react to electrical stimulation. Furthermore, curarized ganglion cells can still be made to discharge by potassium salts.[38]

That a lack of potassium is not the primary cause of symptoms in all

patients with this condition is suggested by the observations that not all cases respond to administration of the ion[30, 32] and that low concentrations of potassium in otherwise normal persons may not cause paralysis.[30] Generally the administration of potassium in the interval between attacks diminishes their frequency, but Seed[39] has reported a case where liberal amounts of potassium given every day, even when the serum level was normal did not prevent seizures. Another disturbing fact is that in one series of patients there was a normal or even slightly elevated concentration of serum potassium.[30]

Since it is not absolutely certain that a deficiency of potassium at the neuromuscular junction is responsible for periodic paralysis, other investigators have studied the metabolism of this element in the muscle cell itself. Concomitant variations in other body chemistry have also been studied.

It has been found that the drop in serum potassium is often accompanied by a fall in serum phosphate,[40] yet repeated studies have shown that the urinary excretion of both these compounds decreases prior to and during the attack.[8, 40, 41] No evidence of renal disease has been found in these patients, and it is most likely that the decreased excretion merely reflects a lower serum level. Since there is no loss of phosphate or potassium from the body during paralysis, the changes observed must be due to an internal shift.[42]

Disturbances in the contraction of muscle cells might well occur if there is an abnormality of metabolism within the cell itself. It has been shown that potassium is essential for the actual mechanical activity of muscle,[19, 43] and the question arises whether the defect in periodic paralysis lies in this sphere. Fenn[44] showed that glycogen is not deposited in the liver without potassium, and this may also be true of muscles. Following muscular activity the serum potassium and lactic acid increase, the concentration of these substances also rises in the liver, and lactic acid is converted to glycogen.[19] After injection of insulin the serum phosphate decreases and that of muscle increases.[40, 26] The muscle content of hexosemonophosphate also rises, and with these changes there is a concomitant fall in serum potassium.[19]

Glycogen in muscles is used partly as a source of energy for the generation of energy-rich phosphate-organic compounds such as phosphocreatine and adenosine triphosphate. When these compounds are hydrolyzed to inorganic phosphate, energy is liberated for the actual contraction. Resynthesis of these compounds does not take place without potassium. The fall in serum phosphate after the injection of insulin or adrenaline, or after the ingestion of glucose is accompanied by a rise

of this compound in muscles. This suggests that phosphate is needed in muscles for phosphorylation and the formation of hexosemonophosphate. Since potassium is also needed for these processes one would expect a corresponding drop in the serum level of this substance, and it has been shown that phosphate, potassium and glucose do tend to migrate together to and from the blood.[19] One theory summarizes these and other facts to explain periodic paralysis. If one assumes that muscle glycogenesis and glycogenolysis cause an increased demand for potassium, and if the deficit of the element causing the actual paralysis is in the muscle cell itself, then it is possible that phosphorylation, etc. requires so much potassium that not enough is left over to resynthesize the high-energy phosphate systems.[19, 42] This is tenable enough if all cases show definite changes in the amount of available potassium, but exceptions have already been mentioned.

In the face of conflicting data relating to the metabolism of potassium in peripheral nerves, myoneural junction and muscle cell itself, some workers have considered this disease to be primarily central in origin. Evidence which supports these contentions cannot be omitted from a general review of literature on the pathogenesis of periodic paralysis. In 1938 Pudenz and others[26] studied a patient who was having a typical attack. The arterial supply of an extremity was occluded and potassium chloride was injected into the venous circulation of the opposite extremity. They noted complete return of function even in the arm which had the arterial supply shut off. Ravina,[27] in 1939, injected the same solution into the brachial artery of a patient with acute paralysis. The venous return of the arm was occluded so that the potassium was concentrated in the area. Despite the high concentration of the ion, no return of function was noted. Suggestive as these experiments are, they still do not explain why only the motor system should be involved in this disease. Watson[45] reported a case with moderately severe attacks in whom an electroencephalogram was normal. His patient had a normal potassium level during the seizure, but a tracing done on our patient, who definitely showed a hypokalemia, was also normal.

Finally, consideration must be given to the role of the thyroid in this disease. In the light of foregoing data is it possible that hyperthyroidism may aggravate existing cases of periodic paralysis or bring forth a latent tendency by effecting potassium metabolism generally or in some way altering the intrinsic responses of muscle cells. Most observers have definitely concluded that thyrotoxicosis makes these patients worse, but a group studied by Wolf[30] showed quite the opposite response. They were not helped by potassium, but thyroid substance gave marked

improvement in most of the family. Dunlay and associates[46] recorded that their patient with thyrotoxicosis was not helped by potassium chloride intravenously. The observations that periodic paralysis comes on at puberty, tends to regress with age and decreases during pregnancy suggests that the disorder is related to a primary endocrine disorder. Wolf[30] feels that attacks of paralysis are precipitated by recurrent bouts of thyroid inadequacy and that development of a goiter during the course of the disease merely represents a compensatory hyperplasia of the gland. It has been shown that the thyroid hormone is an antagonist of most of the secretions of the pancreas.[47] Thus, if it is postulated that there is a disorder in muscle carbohydrate metabolism which requires more than the usual amounts of glucose, phosphate, insulin, and potassium, it is conceivable that the thyroid might become hyperplastic to counteract the effects of chronic pancreatic overstimulation. Or, if this disorder results from any borderline abnormality of the glands of internal secretion, the concept of recurrent endocrine failure is attractive. Such a precarious balance could easily be upset by many factors. Scarlet fever, typhus fever, acute otitis, upper respiratory infections, acute nephritis, exposure to cold or dampness, exertion, prolonged bed rest, menstruation, emotional stress, and diarrhea are all factors which have precipitated attacks in susceptible individuals.[8] It is hard to see how these conditions could cause significant variations in potassium, and it is more likely that they are just the additional stimuli which overbalance one side of a metabolic equation.

In consideration of whether thyrotoxicosis *per se* has any appreciable effect on the level of serum potassium, Pedersen et al. investigated fifteen patients and found no variation from normal in some cases during crises and in others pre-and postoperatively. Furthermore, since the thyroid tends to mobilize glucose from glycogen,[42] since potassium shifts with sugar,[44] and since thyrotoxic patients often show a mild hyperglycemia, one would not expect a low serum potassium and paralysis as a direct consequence of the endocrine disorder.

There is no doubt that our patient had a marked thyroid dysfunction, but if it be assumed that the paralysis observed on the first entry was the result of secondary thyroid failure, an explanation must be sought for the fact that he seemed very resistant to the measures used to lower his potassium and cause paralysis on his second entry. Boekelman[48] has found that when hyperthyroid patients are given a diet low in potassium the concentration of this element in the red blood cells falls, and so does the metabolic rate. He feels that the intracellular potassium regulates the metabolic rate and that there is an antagonistic relationship between serum

iodine and potassium. Thus, if there exists a low intracellular concentration of potassium, there is also an excess of iodine in the intercellular fluid, and the thyroid will compensate with hyperplasia in an attempt to remove the extra I_2. Under such circumstances and if the thyroid is able to handle the surplus iodine it would be more difficult to depress the level of potassium. Also, if the patient had built up his reserves of potassium in the interval, the balance between muscle, thyroid, potassium, iodine, phosphorus, etc., may have been greatly stabilized.

The findings in our patient point again to the fact that periodic paralysis is a widespread disorder. It cannot safely be said that the primary etiology is a disturbance in the handling of just one electrolyte, nor can the pathology be localized to a specific area such as the myoneural junction or the muscle cell. It is more probable that liver, pancreas, thyroid, and the whole neuromuscular system are involved.

SUMMARY AND CONCLUSIONS

1. A case of periodic paralysis with associated hyperthyroidism has been presented.

2. The paralysis was accompanied by a low serum potassium, and the patient responded well to administration of this ion.

3. An attempt has been made to correlate the clinical and laboratory findings in this case with some of the more recent theories on the pathogenesis of periodic paralysis. The possible role of the thyroid is discussed.

4. The shock-like picture and lower cranial nerve involvement presented by this patient on entry emphasize the emergency nature of periodic paralysis in some instances. The need for immediate potassium therapy is obvious, though not all cases respond equally well.

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Syndrome of the Anterior Spinal Artery

A. Theodore Steegmann, M.D.

THIS report is based upon the clinical study of six cases of anterior spinal artery syndrome. An analysis of the symptomatology in the light of present neuroanatomic knowledge is presented. The differential diagnosis and relationship of prognosis to modern treatment justifies a review of the total problem.

The first description of a case of anterior spinal artery thrombosis is credited to Preobrashenski.[1] In 1909 Spiller[2] published careful clinical and pathologic observations on a case, and established the fact that thrombosis of the anterior spinal artery produces a characteristic clinical picture that can be recognized without autopsy. It consists of paralysis of sudden or rapid onset, accompanied by loss of the perception of pain and temperature below the level of the lesion in the spinal cord and by disturbance of bladder and bowel function. The type and degree of paralysis varies with the level of the lesion. There is no impairment of vibratory or position sense.

The interpretation of clinical signs becomes clear when the essential anatomy is understood. The circulation of the spinal cord was worked out in detail by Kadyi.[3] More recently, Suh and Alexander[4] and Herren and Alexander[5] have added details to the anatomy of the intrinsic vascular patterns of the spinal cord. Tureen[6] investigated the resistance of the spinal cord to ischemia. The spinal arteries at the upper level of the spinal cord are derived from the vertebral and ascending cervical arteries. In the thoracic region blood is received from the costovertebral vessels and in the lumbar region, from the dorsal rami of the lumbar arteries. These vessels form branches that enter the vertebral foramina as radicular arteries. The radicular arteries enter with the spinal nerve roots and, after giving off tributaries to the bony and ligamentous structures, accompany

From the department of neurology of the University of Kansas School of Medicine, Kansas City, Kansas.

the spinal nerve roots into the spinal canal as lateral spinal arteries. After penetration of the dura each artery divides into anterior and posterior branches which accompany the corresponding nerve roots; these are the *anterior* and *posterior radicular arteries*. The entire spinal cord derives its blood supply from six to eight anterior radicular arteries and five to eight posterior radicular arteries (figure 1). These enter the nerve roots between the third cervical and the third lumbar segments. At the uppermost level of the spinal cord vessels spring directly from the vertebral arteries to descend and join the anterior spinal trunk. The radicular arteries do not accompany every nerve root but average about one vessel to every second root. The lateral spinal artery may give a branch to only one of the spinal nerve roots at a given level. The largest radicles are found in the upper lumbar area. The anterior radicular arteries are larger than the posterior ones. The anterior radicular arteries supply the *anterior arterial trunk* commonly called the *anterior spinal artery* which runs longitudinally along the anterior median sulcus the entire length of the spinal cord (figure 1). In contrast to this large single anterior lying trunk, the posterior radicular arteries form a pair of posterior spinal trunks, or arteries, which run longitudinally along the posterior portion of the spinal cord on each side adjacent to the entrance zone of the posterior spinal roots. They have numerous anastomatic branches and provide good collateral circulation to the posterior portion of the spinal cord. The lateral and anterior circumference of the spinal cord is supplied by anastomatic coronal vessels, derived from the anterior and posterior arterial trunks, which form a network over the surface (figure 2).

The anterior spinal artery gives off many sulcal branches which enter the central gray matter and anterior horns and divide into penetrating branches that supply the white substance of the lateral and anterior columns. There are no anastomoses between these central vessels and the peripheral arteries. The sulcal arteries arise as independent branches from the spinal trunk and supply either the right or the left side of the cord. Each branch enters at a different level as a rule and they do not alternate regularly. The anterior spinal artery and its penetrating branches act as end arteries and if occluded are followed by a myelomalacia of the anterior half or more of the spinal cord. This is not true of the posterior spinal arteries which have more collateral circulation and if occluded are less likely to give rise to extensive softening. The important cellular areas and tracts supplied by the anterior spinal artery are shown in figure 2. Complete thrombosis results in damage to the central gray matter, anterior horns, and the anterior and lateral columns. The white columns contain the important spinothalamic and the corticospinal tracts.

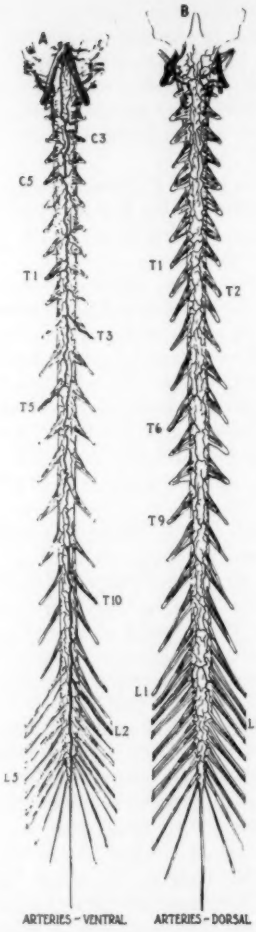

FIG. 1. *(left)* Arteries of the human spinal cord. The major radicular arteries are shown at labeled nerve roots. A: anterior surface showing anterior spinal trunk. B: posterior surface showing paired posterior spinal trunks (After Suh and Alexander).

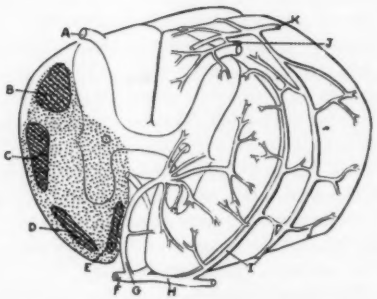

FIG. 2. *(above)* Schematic diagram to show the arterial supply of the spinal cord and areas deprived of blood by occlusion of the anterior spinal artery (stipples). Modified after Herren and Alexander. A, Posterior nerve root. B, Lateral corticospinal tract. C, Lateral spinothalamic tract. D, Ventral spinothalamic tract. E, Ventral corticospinal tract. F, Anterior spinal artery or trunk. G, Anterior sulcal artery. H, Ventral radicular artery. I, Anastomosing plexus of coronal arteries. Most of these vessels join the anterior spinal arterial trunk and have only a third the diameter shown here. J, Dorsal radicular artery. K, Posterior spinal artery or trunk.

The posterior horns and columns get their blood supply from the posterior radicular and spinal arteries.

REPORT OF CASES

Case 1.—A 38 year old woman was admitted to the University of Kansas Medical Center on March 29, 1949 and was dismissed on May 27, 1949. Her illness began on March 4, 1949 with sudden severe cramping pain in the right thigh and leg. Within an hour the right lower extremity was completely paralyzed except for slight movement of the right foot. Weakness had begun in the left lower extremity. The family physician

saw patient soon after development of paralysis and found that in addition to complete paralysis of the lower extremities there was anesthesia to pain and temperature. Paresthesias were present upon scratching the right leg. She was unaware of burns on feet and buttocks from a hot water bottle. There was urinary retention requiring catherization and loss of bowel control. Spontaneous sharp pains in the region around the rectum, inguinal folds, and along both inferior costal margins were aggravated by attempts to sit up.

There was no history of a primary infection. The patient had had a miscarriage at five months following an automobile accident in 1939. She has 3 living children, the youngest 13 years of age. The blood Kolmer and Kahn tests had been found to be positive in December 1948. The family history was non-contributory.

The physical examination was normal except for neurologic changes. Blood pressure was 110/70 mm. Hg. Neurologic examination of the cranial nerves and upper extremities was entirely normal. The lower abdominal muscles were weak and the umbilicus deviated upward on flexing the neck. The lower abdominal skin reflexes were absent. Both lower extremities were partially paralyzed, more pronounced on the left side. Muscle tone was reduced on the left. The deep reflexes were hyperactive bilaterally, and Babinski's sign was positive on both sides. Perception of pinprick, heat and cold was abolished below the tenth thoracic dermatome on both sides, including the saddlezone. Light touch was moderately impaired over the same area, but there was no loss of vibration and position sense. Urinary retention was still present.

Routine blood counts and blood chemistry were normal. The urine contained a trace of albumin, motile bacteria, and a few pus and red blood cells per high power field. The blood Wassermann was 4 plus; Kahn, 3 plus. The cerebrospinal fluid pressure was 170 mm. of water and the dynamic tests normal. The fluid was clear, contained 7 white cells and 1 red blood cell per cu. mm. The Pandy was 1 plus; total protein, 428.4 mg. per 100 cc.; Wassermann negative.

Roentgenograms of the entire spine revealed minor hypertrophic changes and a slight compression of the seventh thoracic body.

Clinical Course.—The return of motor power in the lower extremities was slow but gradual, and the patient was able to walk a short distance by May 19, 1949. The limbs, however, became spastic with bilateral exaggerated reflexes and sustained ankle and patellar clonus. This was more pronounced on the left. Since December 1949 the patient has been able to walk a half mile (805 meters) without tiring. There was some recovery of lower abdominal muscle weakness. The sensory change became less pronounced but stationary after the first few weeks in the hospital. The spinal fluid, examined on May 6, 1949, was entirely normal except for a total protein of 150 mg. per 100 cc., and this had diminished to 24 mg. per 100 cc. when examined in September 1949. Three cystometrograms were made and the results are shown in figure 3. Initially there was a shock reaction with an atonic neurogenic bladder. The patient could not detect heat, cold or pain. On May 10, 1949 she could feel some pain but not heat and cold, and uninhibited contractions were present. Voluntary voiding returned on May 6, 1949, 64 days after the onset of bladder disturbance. On May 10, 1949 the bladder capacity was more than 850 cc. On September 11, 1949 the patient was still unable to differentiate heat and cold, and reflex contractions were of increased intensity. Voluntary effort was poor. There was 60 cc. of residual urine. In December 1949 the patient reported that she could go three hours between voidings and could sometimes go all night without getting up. She still had occasional pains in the low back and lower

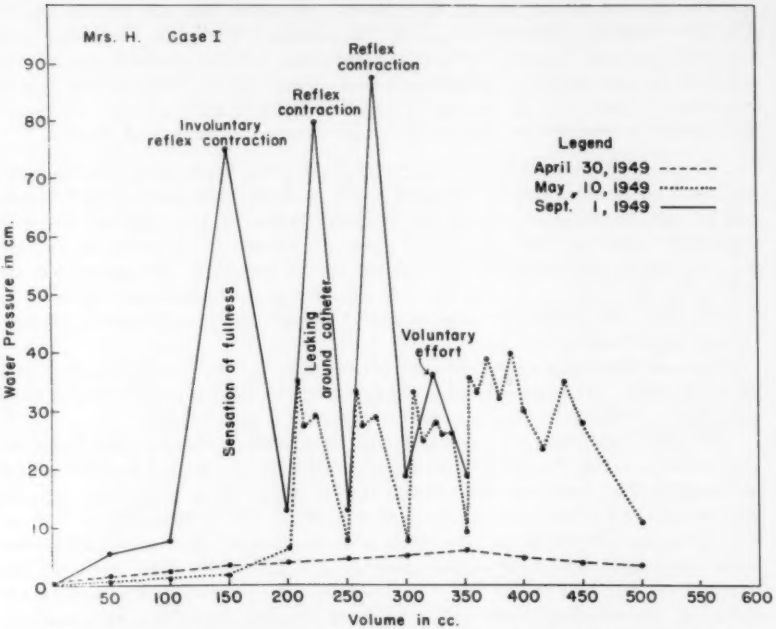

FIG. 3. *Case 1.* Cystometrograms. The initial atonic bladder regained its tone with uninhibited involuntary contractions. Perception of heat and cold was impaired.

extremities. Treatment consisted of preliminary intramuscular injections of bismuth subsalicylate (1.5 cc. at five day intervals) followed by 10.2 million units of penicillin intramuscularly (Depocillin, 600,000 units daily). Continuous catheter drainage with sterile boric acid irrigations was maintained until voluntary micturition returned.

Comment.—This case is a typical example of thrombosis of the anterior spinal artery. Syphilitic arteritis was the probable etiology. The degenerated area in the spinal cord extended from the tenth thoracic to the first lumbar segment. Pain at the onset occurred in the right thigh, which corresponds to a level of the cord just below the lower level of softening. Later the patient had pain in the upper abdomen corresponding to a level in the cord just above the zone of softening. The rapid onset of paraplegia with anesthesia to touch, pain and temperature below the tenth thoracic segment denotes interruption of the corticospinal and spinothalamic tracts in the lateral and anterior columns. The initial disturbance of bowel and bladder function was the result of spinal shock. Weakness, loss of tone and reflex responses of the lower abdominal muscles followed degeneration of the anterior horns of the lower three thoracic segments. Why thrombosis of the anterior spinal artery did not extend beyond those three segments probably depends upon the level at which radicular arteries above and below the lesion furnish tributary circulation to the main trunk. Myelomalacia presumably involved the anterior half of the spinal cord high enough in the lateral columns to produce partial degeneration of the pyramidal tracts. Partial sparing of the lateral

spinothalamic tracts may depend on collateral circulation from the coronal vessels. The poor prognosis reported in cases of this syndrome in the past depended upon secondary ascending urinary tract and skin infection. A better prognosis can now be predicted by more effective treatment of urinary tract infection. Skin infection can be controlled by good nursing care and cleanliness. Early physical therapy and motor rehabilitation procedures are necessary to obtain maximum restoration of function.

Case 2.—A 50 year old white man was admitted to the University of Kansas Medical Center on June 5, 1949 and dismissed on July 2, 1949. Three weeks prior to admission he had developed a dull pain in the lower abdomen. This persisted and four days before admission there was a rapid onset of numbness and weakness in the right lower extremity which began in the thigh and spread downward. The patient was unable to flex the right knee off the bed. This was followed by weakness and numbness of a less severe degree in the left lower extremity. Urinary and bowel retention occurred two days before admission.

Past medical history was not relevant. He had dislocated his left shoulder 18 months previously which left some residual numbness along the ulnar border of the left hand and forearm. Nocturia once a night had been present for some months.

Physical examination was normal except for neurologic changes. Blood pressure was 115/65 mm. Hg. The right pupil was larger than the left and the reaction to light was sluggish. The fundi appeared normal, and no cranial nerve defects were present. The strength and muscle tone in the upper extremities were normal and the deep reflexes physiologic. There was a hypesthesia to all qualities of sensation along the ulnar border of the left hand. Both lower extremities were spastic, the right very weak but strength was adequate on the left side. Abdominal skin reflexes were absent on the right. The patellar reflexes were brisk, more so on the right; the achilles reflex was sluggish on the right and absent on the left. Babinski's sign was positive bilaterally. Perception of pinprick was absent below the fifth thoracic dermatome on the right and below the tenth thoracic dermatome on the left. Below the mid-thigh on the right, pinprick could again be felt. Light touch was slightly impaired in the corresponding areas. It was most defective between the right sixth and tenth thoracic dermatomes. Vibratory sense perception was reduced at the ankles, more on the left, and position sense was defective in the toes. The heel to knee test revealed ataxia, more pronounced on the left side where motor function was better retained.

The urine showed a trace of albumin, disintegrated pus cells, and numerous bacteria, the latter E.coli by culture. Routine blood counts and blood chemistry were normal. The blood serodiagnostic test was reported as 64 Kolmer units and 10 Kahn units. The cerebrospinal fluid was under 90 millimeters of water pressure, its color was slightly xanthochromic, and dynamic tests were normal. There were 22 white blood cells per cubic millimeter, 95 per cent lymphocytes. The Pandy was 4 plus; total protein, 1.4 gm. per 100 cc. The cerebrospinal fluid Wassermann was negative. Another spinal fluid examination on June 13, 1949 revealed a clear fluid with 19 cells, all lymphocytes, per cu. mm. The total protein was 58.5 mg. per 100 cc.; colloidal gold, 001221000; Wasserman, negative. Roentgenograms of the spine revealed moderate osteoarthritis of the lower dorsal bodies.

Clinical Course:—The patient was placed on catheter drainage and a cystometrogram on June 13, 1949 indicated a normal functioning bladder (figure 4). Panendoscopic examination exhibited a vesical neck contracture with retention which was

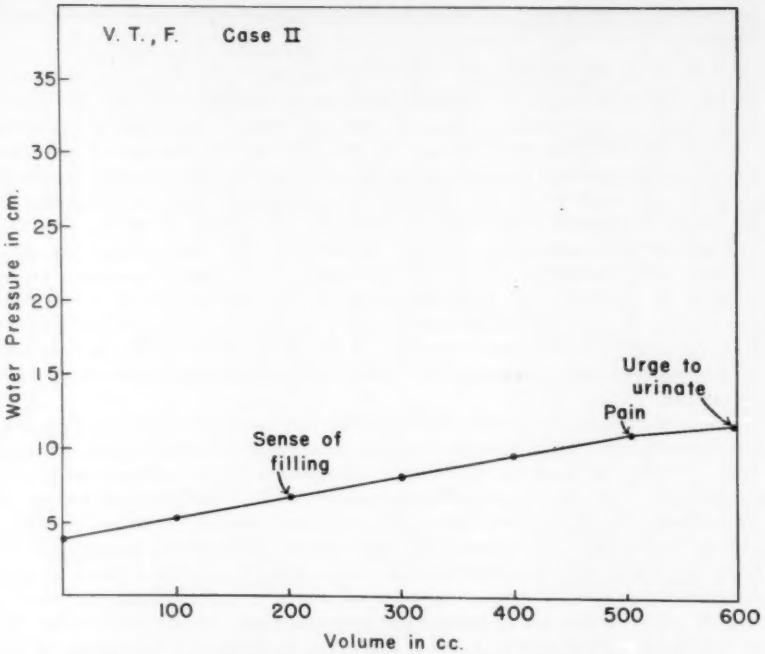

FIG. 4. *Case 2.* Cystometrogram normal but patient had vesicle neck contracture.

thought to have been precipitated by the spinal vascular lesion. The patient refused transurethral resection but regained bladder control about June 22, 1949. Pain in the lower abdomen gradually subsided and motor strength improved. Sensory changes were less marked but persisted over the same distribution. The patient received 10 million units of penicillin which reduced his blood serology from 64 to 32 Kolmer units by June 27, 1949. A report from the patient, dated December 27, 1949, stated that weakness was still present in the lower extremities, but the patient was able to walk approximately a quarter of a mile (400 meters). He did not report any noticeable sensory changes in the lower extremities. He can go three to four hours between micturitions.

Comment:—Long duration of pain before onset of paralysis has been reported in cases of intraspinal hemorrhage. In this case thrombosis seemed more probable. The unequal sluggish pupils, loss of achilles reflexes, disturbed vibration and position sense in the feet were accepted as evidence of cerebrospinal syphilis, present prior to the vascular accident in the spinal cord. The sensory changes extended upward five segments higher on the right than the left side. This can be explained by assuming that collateral blood supply to the spinothalamic tract, perhaps from anastomosing coronal vessels on the right side, prevented softening of the anterior lateral column at the same level on each side. If hemorrhage rather than thrombosis is assumed to have occurred, bleeding along the right posterior horn could explain the sensory step. Vesical neck

contracture developed after the initial retention and was contributed to by the spinal lesion.

Case 3.—A 60 year old white woman was admitted to the University of Kansas Medical Center on August 11, 1949 and dismissed on September 28, 1949. Her illness began early in the morning on August 5, 1949 with sudden severe pain in the lower cervical region radiating around the neck to the upper sternum. Paralysis of both arms and legs started within ten minutes and at the end of thirty minutes she was completely paralyzed and could not control bladder or bowel function. There was no dulling of her senses, or difficulty in breathing or swallowing. By evening of the day of onset, she had recovered some ability to move the left foot. The next morning she could flex both lower extremities and the left arm weakly. At the time of admission to the hospital, the right arm was completely paralyzed and weakness in the other limbs was present. Enemas and catheterization were necessary. She developed an irregular fever up to 100° F. with some sweating and occasional vomiting. Her past medical history had been uneventful except for ankle edema at times and moderate dyspnea on exertion.

General medical examination revealed slight liver enlargement and a blood pressure of 120/80 mm. Hg. Neurologic examination on August 12, 1949 showed no cranial nerve defects except deafness which was of the conduction type and more marked on the left side. There was complete flaccid paralysis of the right arm with loss of all deep reflexes. The patient could flex weakly but not extend the left arm at the elbow and the deep reflexes were absent. The deep reflexes in both lower extremities could barely be elicited, and the abdominal skin reflexes were absent. There was a positive Babinski sign bilaterally. Any manipulation of the right arm and neck was painful, and the lower cervical and upper thoracic spine was tender to palpation. There was no loss of light touch perception but pinprick was impaired over the dorsum of the right hand and forearm and over the radial side of the left hand. Heat and cold could not be differentiated in corresponding areas.

The urine contained 20 to 30 pus cells per high power field but was otherwise normal. Blood counts were normal but the hemoglobin was 11 grams (71 per cent). Blood Wassermann was negative. The blood chemistry was normal. Cerebrospinal fluid was slightly xanthochromic, under 140 mm. of water pressure, and without evidence of subarachnoid block. The fluid contained 8 white blood cells and 165 red blood cells per cu. mm. The colloidal gold curve was flat. There was 156.2 mg. of total protein per 100 cc., and a negative Wassermann reaction.

Clinical Course:—The patient gradually regained strength in the arms and legs, recovery being slowest in the right arm. A cystometric examination on August 13, 1949 indicated an intact sensory arc, but the motor arc was somewhat weakened (figure 5). The patient developed voluntary control of urination about August 21, 1949. A second examination made on September 1, 1949 disclosed normal adult bladder function. Weakness of all muscle groups of the right upper extremity and some atrophy was still present on August 28, 1949. The patient could open and close the fist but not flex or extend the arm at wrist or elbow. The left arm was stronger with moderate strength in all groups except the left triceps which was still weak. Muscle tone was absent in the right arm but had returned in the left arm. The deep reflexes were absent in the right arm, except for a weak triceps response, and hyperactive in the left arm. Both lower extremities had considerable strength but deep reflexes were hyperactive.

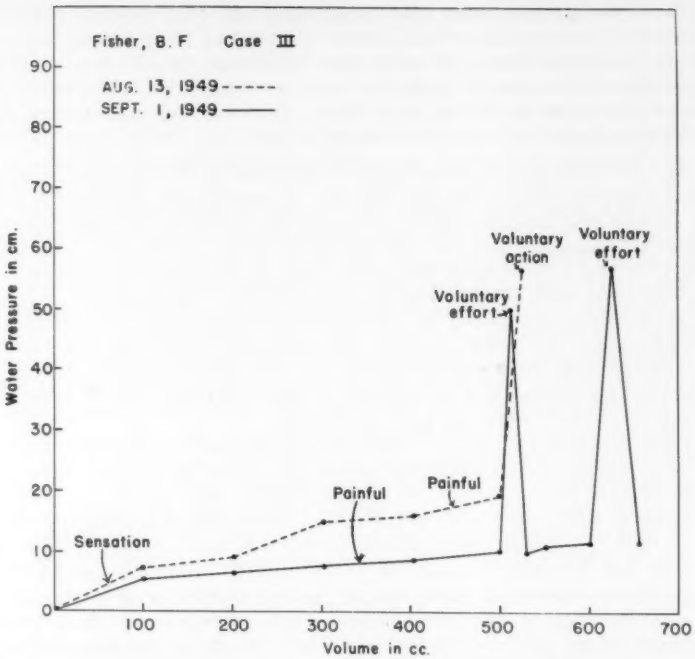

FIG. 5. *Case 3.* Cystometrograms normal but some initial motor weakness.

The abdominal skin reflexes were absent on both sides and a bilateral Babinski sign was present. Manipulation of the neck and right arm was still painful. A segmental zone of hyperesthesia to pinprick extended along the ulnar side of the right hand and arm, across the chest, and down the inside of the left arm to the elbow. Thermal perception and differentiation was impaired over the outer aspect of the right upper arm and shoulder, but touch, vibration and position sense were unimpaired. At the time of dismissal on September 25, 1949, movement of all muscle groups had returned in the right upper extremity but strength was impaired. The deep reflexes, except the brachio-radialis, were absent. The other extremities had fairly good strength but were spastic. Babinski sign was present only on the right. She was unable to walk alone. The zone of hyperesthesia to pinprick was confined to the right inner arm; tenderness of the second and third posterior thoracic spinous processes persisted.

Comment:—This patient, seven weeks after the onset of her illness, had rather severe upper motor neuron weakness of the left arm and both lower extremities. There was lower motor neurone weakness and some atrophy of the right upper limb. The sensory changes were segmental in character, and the spinothalamic tracts were not interrupted. Damage to the cord was restricted to the central gray matter and right anterior horn for a few segments and to the descending pyramidal tracts. It can again

be assumed that the spinothalmic tracts lying peripherally were protected by collateral circulation of anastomosing coronal arteries. The amount of protein in the spinal fluid was less than in the first two cases where the damage occurred at a lower level. The spinal fluid, as in case 2, was slightly xanthochromic, yet the history and clinical observations were similar to those made in proved cases of occlusion of the anterior spinal artery. Bladder retention recovered in 16 days.

Case 4.—A 65 year old colored male was admitted to the University of Kansas Medical Center on May 9, 1945 and dismissed on June 9, 1945. He dated his illness from April 30, 1945 after exposure to cold which was followed by an upper respiratory infection and tingling of both shoulders and arms. After apparent recovery he awoke on May 4, 1945 with occipital headache, dizziness and nausea. He noticed some staggering in gait while going to work but worked all day. That evening he developed tingling and dragging of his left leg. This progressed until walking was difficult. The following morning both lower extremities were weak, and the left arm was numb and weak. He had difficulty in voiding. For the next two or three days paralysis of the left arm and leg increased and was followed on May 8, 1945 by paralysis of the right arm and leg and by bladder and bowel incontinence.

The patient denied a history of syphilis. His left eye had been blinded by a powder burn some years before. He stated that he had had asthma and influenza followed by pleurisy in 1918. He had nocturia five or six times each night for several months.

On examination, coarse moist rales were heard at the base of the lungs posteriorly; the heart was not enlarged but a systolic murmer was heard at the apex and over the aortic area. The blood pressure was 140/90 mm. Hg. Neurologic examination on May 13, 1945 showed small pupils, the left inactive to light; optic atrophy on the left; advanced retinal arteriosclerotic changes; and slight reduction to the perception of pinprick on the right side of the face. There was almost complete absence of diaphragmatic breathing. The left arm and leg were paralyzed, the degree being greater in the arm; the abdominal skin reflexes and deep reflexes were absent and the Babinski sign positive. On the right, the arm and leg were paralyzed but the deep reflexes, although sluggish, could be elicited. The abdominal skin reflexes were not abolished and the Babinski sign was equivocal. The perception of pinprick was lost on the right side below the fourth thoracic dermatome. There was no sensory loss to touch or other qualities.

Laboratory examination showed a trace of albumin in the urine; normal blood counts and blood chemistry; blood Wassermann and Kahn negative. The chest roentgenogram was normal, and electrocardiogram normal except for evidence of auricular strain.

Clinical Course:—The patient improved somewhat by the time of his dismissal from the hospital. He could voluntarily move his right arm and leg, but incontinence persisted.

The patient was readmitted to the hospital on May 16, 1947 and dismissed June 14, 1947. He had had hematuria several times during the preceding month. The urologist could find no cause for this except urethral irritation from the catheter. His blood pressure was 170/90 mm. Hg. Peripheral and retinal arteries were markedly sclerotic. There was generalized muscular atrophy of the upper extremities, especially in the forearms, and the left hand showed thickened nails and hyperkeratotic skin. Flexion contractures were present in the right elbow, and there was atrophy and desquamation of the skin of the lower extremities. Decubitus ulceration was present

in the left popliteal fossa. The deep reflexes were universally hyperactive and abdominal reflexes absent. The feet were drawn down by plantar flexor contractures so that the plantar responses could not be evaluated. The upper extremities were weak; the patient could not move hands or wrists, and ataxia was present in arm movements. The right lower extremity was weak, the left paralyzed. The patient could not voluntarily control his bladder but bowel control had been regained. There were no tangible sensory changes. The patient was bedridden and unable to feed himself. He had pyuria and secondary anemia.

Roentgenograms revealed evidence of arteriosclerosis of the aorta and other large vessels and hypertrophic arthritis of the spine. The patient died on December 24, 1947.

Comment:—An arteriosclerotic thrombosis of the anterior spinal trunk from about the fourth cervical segment downward to the first thoracic segment of the spinal cord was considered the etiology of this case. The onset was rather slow with paresthesias in the arms and shoulders but no pain. The sensory changes below the right fourth thoracic dermatome were mild and of short duration, but motor paralysis was severe and irreparable. The diaphragmatic paralysis points to midcervical damage. Atrophy in the arms indicates anterior horn degeneration, and paralysis of the lower limbs was of pyramidal tract origin. The severe contractures and deformities had resulted from inadequate manipulation and stretching of the paralyzed limbs after dismissal from the hospital. This case is another example of recovery of sensory changes but severe degeneration of the structures supplied by the anterior sulcal vessels. The patient's severe paralysis made the return to a useful existence impossible. His long survival in the face of constant urinary infection is an amazing example of human resistance.

Case 5:—A 63 year old white male was admitted to the University of Kansas Medical Center on August 10, 1945 and dismissed on August 16, 1945. Two weeks before admission, after a day of hard manual labor, the patient noticed tingling in his lower extremities. Within a few days his limbs became numb and he experienced pain, not of the girdle type, radiating upward from both costal margins. Within a week an associated weakness in the legs developed more on the right, necessitating a cane for assistance in walking. Four days before admission bladder and bowel control was lost, and two days later he was unable to walk. The patient complained of intermittent, dull lower abdominal pain. He had abdominal distention and was barely able to move his right leg. Past history was irrelevant.

Physical examination was normal except for neurologic changes which were confined to the trunk and lower extremities. Abdominal tenderness was present above the pubis, and the bladder was distended. The patient was able to flex the left lower extremity at the hip to about 10 degrees above the bed, but was unable to move the right leg except the toes. The lower limbs were spastic to passive motion; the deep reflexes were reduced in the left lower extremity but brisk on the right with transient ankle clonus. Babinski's sign was positive on both sides. The abdominal skin reflexes were absent. There was partial loss of perception of pinprick and light touch below the fifth thoracic dermatome on both sides. Vibratory sense perception was diminished below the knees and there was some position sense impairment in the toes. The prostate was moderately enlarged and rectal tone was reduced.

Examination of the urine, blood and cerebrospinal fluid were all normal. There was no evidence of spinal subarachnoid block by dynamic tests and by pantopaque myelagraphy. Spinal roentgenograms showed extensive hypertrophic arthritic changes.

The patient was dismissed from the hospital after diagnostic study, with his condition unchanged. A report from him dated January 10, 1950 stated that he still had weakness in his legs and could only walk a short distance. He was still unable to control his bladder, but reported that the sensory defects recovered within a year after the onset of his illness.

Comment:—The slow onset in this case with severe pain resembles cases of proved central hemorrhage in the spinal cord, but thrombosis cannot be excluded by any evidence found. Myelography was carried out to exclude a spinal cord tumor. In contrast to the other cases reported here, the absence of elevation of the cerebrospinal fluid protein is of interest. The reduction of vibration and position sense below the knees in elderly Kansas farmers is frequently found here and was not considered the result of the last illness. Impairment of touch may have been the result of anterior spinothalamic tract interruption. The etiology is ostensibly of arteriosclerotic origin.

Case 6.—A 14 year old school girl was admitted to the University of Kansas Medical Center on December 5, 1945 and dismissed on December 13, 1945.

On November 22, 1945 she became ill with what was believed to be a mild upper respiratory infection characterized by a cough and malaise but without fever or sore throat. She returned to school on November 28, 1945 but had to return home because of weakness in her legs. The situation remained the same until December 2, 1945 when she went to bed complaining of pain in her legs and awoke at 3:00 A.M. with numbness and paralysis of both lower extremities and inability to void. Bowel action was not impaired. On the day of admission to the hospital the numbness seemed less marked but she complained of pain in her right lower thorax.

The only event in the past history of questionable importance was a fall on the buttocks six weeks before, resulting in soreness of the lumbar muscles for a few days.

The patient was not acutely ill, but she had a red throat and anterior cervical adenopathy. The chest was normal except a few fine rales heard at both bases. The cranial nerves and upper extremities were normal. The bladder was distended to the level of the umbilicus. The lower limbs were lying in external rotation, and she was barely able to flex the knees and hips; hamstrings were tense; the right patellar reflex was brisker than the left; and both achilles reflexes were hyperactive. The right abdominal skin reflexes were absent, the left present. A Babinski sign was present on the right and equivocal on the left. Hypesthesia to pinprick was present below the eleventh thoracic dermatome bilaterally, including the saddle zone, and light touch was slightly impaired over the same area. Vibration and position sense were unimpaired. Tenderness of the lower lumbar posterior spinous processes was noted on palpation.

The initial leucocyte count was 11,050 per cubic millimeter. The blood Wassermann and Kahn were negative. Blood chemistry and urinalysis were normal. The cerebrospinal fluid contained no cells. Globulin test was negative; total protein, 24 mg. per 100 cc.; and colloidal gold, 0111000000. Roentgenograms of the chest and spine were negative with the exception of a cleft in the lamina of the fifth lumbar vertebra near the posterior spinous process, possibly of traumatic origin.

Hospital course was satisfactory and catheterization was necessary for only the first two days. On the second day the patient was able to move her lower extremities freely; numbness disappeared, and she began to void voluntarily. She was able to walk from the hospital on the eighth hospital day. A week after dismissal her family

doctor reported that there was still some weakness of the leg muscles. By the end of the second week she had completely recovered.

Comment:—This case raises some questions that cannot be answered with certainty. Clinically, the syndrome was typical of anterior spinal artery occlusion, but the rapid recovery without residuals was unexpected. The onset of illness, ten days following some type of acute infection, possibly a virus infection, makes it necessary to exclude an acute myelitis or postinfectious neuropathy. The absence of cells in the cerebrospinal fluid and lack of complete transverse cord signs weigh against a myelitis, and the dissociated sensation, segmental cord involvement, pyramidal tract signs, and rapid recovery exclude a neuropathy. The syndrome must have been vascular in origin even though blood vessel damage may have been secondary to infection. The interval of six weeks after apparent minor trauma would seem to minimize the importance of that factor unless it could be assumed that vascular damage was initiated by trauma. Spontaneous central hemorrhage in a vascular anomaly is a possibility, but recovery would seem to be too rapid and the destructive character of blood on cord tissue would be likely to leave residuals. This patient is still well, four years later, a fact that would exclude hemorrhage into a tumor. The assumption of angiospasm, producing temporary ischemia, edema and recovery, is speculative and would seem dubious in a healthy young girl. If thrombosis occurred, the rapid recovery suggests that the collateral circulation may be more efficient in young people. Bladder retention even in mild cases should be emphasized.

GENERAL CONSIDERATIONS

Essential data on the six cases reported here is shown in table 1. Only one case occurred in a young person. The etiology was syphilitic arteritis in two cases, arteriosclerosis in three cases, and infection in one case. There was no sex preference. The upper level of the lesion involved the cervical level of the spinal cord in two cases, and the middle or lower thoracic cord in the remainder. Zeitlin and Lichtenstein[7] reviewed seven cases of anterior spinal artery occlusion, proved at autopsy, of which three involved the cervical spinal cord and the remainder were in the thoracic region. The lesion may extend over only three or as many as fifteen segments. This probably depends upon the distribution of the radicular arteries and upon the degree and type of pathologic changes present in the anterior spinal arterial trunk. Occlusion produces an ischemic myelomalacia. It is of interest that one of Zeitlin and Lichtenstein's patients, a woman 45 years of age without any clinical evidence of vascular disease, showed arteriosclerotic thrombosis at autopsy.

Diagnosis of an anterior spinal artery syndrome rests upon the combination of certain signs that appear consistently. The onset may be sudden or by gradual development over a period of hours. The principle symptoms are as follows:

Pain is the initial symptom in most cases and may be very severe or dull in intensity. It may correspond to a level lying just above the height

of the lesion in the spinal cord or in the level of the cord below the thrombotic zone, Pain may persist long after the state of paralysis, as girdle-like pain or along the spine. Some patients describe tingling or paresthesias, rather than actual pain.

Paralysis is most always incomplete and develops rapidly to its maximum degree within an hour, or more slowly over a period of two or three days. As a rule the paralysis is bilateral but may be more pronounced on one side. Paralysis produced by degeneration of the anterior horns is of the lower motor neurone type with loss of muscle tone, weakness, atrophy and areflexia. It corresponds to the number of spinal cord segments undergoing degeneration. Muscle paralysis below the level of the lesion is of the upper motor neurone type with increased tone, hyperreflexia, clonus and pathological plantar responses. This depends upon interruption of the descending pyramidal tracts, and at the onset leaves the affected muscles in a state of spinal shock. Variations in the clinical picture depends upon the level of the lesion.

Thrombosis of the anterior spinal trunk, near its origin from the vertebral arteries, produces a *medullary syndrome* which was described by Spiller.[8] The syndrome may be unilateral or bilateral and is characterized, if bilateral, by a spastic tetraplegia and loss of discriminative sensation below the level of the lesion. Two such cases have been reported by Davison[9] who found, in addition to the above signs, nystagmus and urinary and fecal incontinence but no atrophy of the tongue.

Involvement of the *cervical spinal cord* produces a flaccid paralysis in the upper extremities, spastic diplegia in the lower extremities with dissociated sensory loss below the level of the lesion.

A lesion in the *thoracicolumbar spinal cord* leads to segmental muscular atrophy corresponding to the zone of softening, spastic paraplegia in the lower extremities, and dissociated sensory loss below the level of the lesion. In some cases the paralysis may be unilateral with sensory loss in the opposite lower limb.

Softening in the *lumbar spinal cord* causes a flaccid atrophic paralysis of the lower extremities with dissociated sensory changes. Spinal shock occurs early in all of these variations of the syndrome.

Sensory changes occur early and may precede or develop along with the paralysis. In thrombosis at the medullary level, there is a loss of discriminative sense perception. At all levels below the medulla, the sensory loss is dissociated, and pain and temperature sense is abolished below the segmental level of the lesion. Light touch may be impaired to some degree but it is not as pronounced as the loss of pain and temperature sense.

If the sensory changes do not disappear within the first few weeks of illness, the loss is permanent but may become mild and not recognized by the patient. The loss of touch perception has been seldom emphasized by writers on this subject although it has been described in their clinical reports. Fibers carrying light touch have two routes by which they ascend upward in the spinal cord. Some ascend uncrossed in the dorsal funiculus and others run ventromedially across the ventral commissure to ascend on the opposite side in the ventrospinothalamic tract.[10] It is the latter fibers that can be interrupted by softening of the anterior white column in anterior spinal artery thrombosis. Position and deep sensibility conducted by the posterior columns are not affected.

Trophic changes in the affected limbs have been described in severe cases. Except for coldness and mottling of the skin, trophic changes were insignificant except in case 4.

Sphincter disturbance is often produced by the spinal shock which usually accompanies the onset of the anterior spinal artery sydrome. Fecal retention occurs at onset but soon recovers in the majority of cases after the regular use of enemas. If residual spasticity is pronounced sphincter spasm may be a permanent residual as in any disease, producing bilateral pyramidal tract defects in which there is inadequate voluntary inhibitory impulses from higher centers and unhibited reflex sphincter tone.

Urinary retention occurs early during the spinal shock stage and requires catheterization. This was present in all six cases. It developed after the onset of sensory and motor changes in case 2 and in case 5. The time of onset was two days later in case 2 and five days later in case 5. In milder cases, such as case 6, voluntary bladder control was regained in four days, probably corresponding to the recovery of spinal shock. In more severe cases, voluntary control was regained in a period varying from about two weeks to over two months. The time of recovery in cases 1, 2, and 3 was 64 days, 19 days, and 16 days, respectively.

Bladder recovery did not occur in cases 4 and 5. Prostatic enlargement was present in case 5. Unfortunately cystometrograms were not available in those two cases and the type of bladder defect is not known. Cervical neck contraction occurred in case 2, but voluntary recovery was regained. In case 1 the bladder, after a primary period of atonicity, regained its tone and became an uninhibited neurogenic bladder, though, with fairly good voluntary control. If bladder dysfunction depends on pyramidal tract interruption, bladder difficulty may be proportional to the damage of those tracts. The recovery of bladder function in this disease follows the same stages of recovery seen in other types of spinal cord injuries described by Holmes[11] Munro[12] and Prather,[13] the type of change in a

TABLE 1

DATA ON 6 CASES OF ANTERIOR SPINAL ARTERY SYNDROME

Case	*Age*	*Sex*	*Probable Etiology*	*Upper Level of Lesion*	*Site of Pain*	*Initial C.S.F. Total Protein*
1	38	F	Syphilitic Arteritis	Thoracic 10	Costal margins Groins Saddle zone	428.4 mg.
2	50	M	Syphilitic Arteritis	Thoracic 5R Thoracic 10L	Lower abdomen	1.4 Gm.
3	50	F	Spinal Arteriosclerosis	Cervical 5	Lower cervical region	136.2 mg.
4	65	M	Spinal Arteriosclerosis	Cervical 4	Paresthesias arms and shoulders	none
5	63	M	Spinal Arteriosclerosis	Thoracic 5	Costal margins Lower abdomen	Glob. neg.
6	14	F	Infection	Thoracic 11	Lower Thorax Lower limbs	24 mg.

given case depending on the degree and extent of spinal injury.

The *cerebrospinal fluid* may show changes. It was examined in five cases with no evidence of spinal subarachnoid block. The total protein level was elevated in the first three cases (table 1). The extent and location of the lesion in the spinal cord may have some influence on the degree of total protein elevation. In case 2 the extremely high value of the total protein in the absence of block is difficult to explain. The extensive length of the lesion low in the thoracic cord, secondary venous hyperemia, or the possibility of hemorrhage in the cord at the onset are possible factors. Total protein determinations were not recorded in cases 4 and 5. The degree of actual cord damage was small and reversible in case 6 and the total protein within normal limits. In the two syphilitic cases serology tests were positive for the blood specimen but negative for the cerebrospinal fluid. The cell count was elevated only in case 2. Slight xanthochromia was present in cases 2 and 3. Whether this was the result of stasis or initial hemorrhage is not known.

Differential diagnosis of anterior spinal artery thrombosis requires the exclusion of a number of conditions that are capable of producing a rapidly developing partial transverse spinal cord lesion. Formerly such conditions were called "acute myelitis" until Bastian[14] pointed out that they were not commonly caused by an acute inflammatory process but were the result of thrombosis of the spinal arteries. A true *acute myelitis* is a fulminating inflammatory disease of the spinal cord. It causes a transverse cord lesion. The etiology is obscure except in those cases in which a

bacterial infection, syphilis or tuberculosis are found. The slow development, ascending tendency, presence of fever or infection, and the loss of sensation to all qualities help to differentiate it from anterior spinal artery thrombosis. Pleocytosis occurs in some cases of acute myelitis.

Epidural abscess tends to produce compression with spinal subarachnoid block. The presence of bone erosion of the spinal vertebra by infection or metastatic carcinoma gives a clue to other processes that lead to dural compression and block.

An *acute encephalomyelitis* can be differentiated by symptoms or signs that indicate involvement of the brain stem or brain. Spiller[15] has emphasized that the spinal radicular arteries may be compressed by tumor tissue adjacent to them, thus giving rise to thrombosis secondarily. The slow progressive course of *spinal cord tumors* with subarachnoid block would not lead to confusion except in rare instances when the radicular arteries are compressed.

Multiple sclerosis developing rapidly with a large focal lesion in the spinal cord can be confused with a vascular lesion unless signs at brain stem or higher levels show the disseminated nature of the process. Pain is uncommon in multiple sclerosis and there is frequently evidence of cerebellar and posterior column defects.

Acute syphilitic involvement of the spinal cord may present baffling diagnostic problems. Observations have been reported by Preobrashenski,[1] Spiller,[2] Adams and Merritt,[16] Margulis,[17] Williamson,[18] Chung,[19, 20] Margaretten,[21] King, [22] Berman,[23] Wexberg[24] and Lindemulder.[25] Adams and Merritt mention the slow progressive course of syphilitic meningomyelitis as contrasted to the abrupt onset with later improvement in syphilitic spinal thrombosis as an important differential characteristic. However, they found that syphilitic meningomyelitis may be complicated by spinal artery thrombosis. Chung expressed the opinion that the posterior spinal arteries are more vulnerable to occlusion than the anterior spinal trunk in syphilis and the veins may also be thrombosed. Many of the cases described as acute syphilitic myelitis are not pure anterior spinal artery syndromes comparable to the two cases of syphilitic arteritis reported here. In both of these cases, the spinal fluid serology was negative and the sensory changes were dissociated. The onset of acute syphilitic myelitis may be rapid but the pathologic changes may not be limited to the anterior spinal artery distribution. The sensory changes involve all qualities of sensation as in a real transverse myelopathy. This should aid in differentiating a transverse myelopathy from anterior spinal artery thrombosis in syphilis. The pathologic process in the vessels in both cases reported here is the same and is probably the pan-arteritis of Heubner.

Spontaneous hemorrhage into the spinal cord, if limited to the central gray matter or anterior regions of the cord, is most difficult if not impossible to differentiate from anterior spinal artery thrombosis. Richardson[26] and Holmes[27] have reported cases and reviewed the subject. They believe that hemorrhage, like thrombosis, may occur suddenly and spontaneously. Richardson thinks that direct trauma has been over emphasized as a cause. Rupture or an intramedullary vascular tumor or anomaly is perhaps the most common cause. Buchanan and Walker[28] have reported such lesions in children. Rupture of blood vessels in syphilis, aneurysm, hemorrhagic diathesis, acute myelitis and arteriosclerosis contribute a small share of the cases. Pain in cases of hemorrhage was recurrent at intervals for hours or days. The symptoms of motor and sensory loss below a segmental level of the spinal cord and sphincter disturbance was rapid in onset as in thrombosis. Recurrent pain, xanthochromic spinal fluid with high protein content, and sometimes spinal subarachnoid block have been found in hematomyelia. Except for block, these are also found in cases of thrombosis. A cutaneous nevus may lead the examiner to suspect a vascular cord anomaly. The observations of Latham[29] shows that hemorrhage is not limited to any region of the spinal cord but occurs in both gray and white matter. The symptoms vary with the region of cord involved. Hemorrhage has some predilection for gray matter, and bleeding may extend up and down the cord, especially along the posterior horns. Hematomyelia has been found to occur most often in young people and is not common in arteriosclerosis with hypertension. Richardson found that the onset of hemorrhage was gradual in some cases and the cerebrospinal fluid may be clear without block. All sensation was lost in some patients but dissociated in others. Sensation is always dissociated in thrombosis. Hemorrhage into the cervical cord causes sudden or rapid death from respiratory failure. At a lower level, recovery may occur with or without residual neurologic changes. In some cases it is impossible to differentiate spinal hemorrhage from thrombosis on the basis of clinical and laboratory studies.

The etiology of occlusion of the anterior spinal artery in the majority of cases depends upon pre-existing disease of the blood vessel wall. Syphilis has been considered the most important disease, but Holmes[27] questions the over emphasis on syphilis and believes that vascular tumors or small aneurysms are more common causes. Direct trauma from yawning apparently produced occlusion in the curious case reported by Grinker and Guy.[30] Indirect trauma by lifting or exertion occurred in cases reported by Spiller[2] and Margulis.[17] Schaller, Roberts and Stadtherr[31] in their report thought hypotension and stasis were important factors in two

middle aged patients not affected with syphilis. No tangible causation was found in cases occurring in relatively young patients reported by Ornsteen[32] and Hogan.[33] Vogel and Meyer[34] in an autopsy-proved case considered embolism as the possible cause of occlusion of the anterior spinal artery. Arteriosclerosis is important in the older age group, and occlusion in any age group may occur spontaneously without any known exciting factor. The lower cervical and thoracicolumbar segments are the regions of the spinal cord most commonly involved.

TREATMENT

In the early stage of the disease the most important treatment procedures are directed towards prevention of bladder and skin infection. Urinary tract infection was the most common cause of death in earlier reports in the literature. Since these patients have only partial degeneration of the spinal cord, the return of voluntary control of bladder function can be expected in the majority of cases. In older male patients, prostatic hypertrophy may be responsible for a poor return of function and transurethral or vesical neck resection may be necessary. Many of the treatment procedures for urologic complications recommended by Prather[13] were carried out. In the stage of spinal shock, when urinary and bowel retention was present, the patients were treated with enemas and continuous catheter drainage by the closed system technique. Intermittent catheterizations should not be done. The bladder was irrigated several times a day with sterile saline or boric acid. Frequent urinalysis and urine culture were made and cystometric tests were done at intervals. As soon as involuntary bladder contraction began to appear, trial voluntary voiding was attempted until voluntary control was established. After voluntary control was re-established, catheterization for the amount of residual urine was done periodically. Fluids were urged, and if signs of urinary infection appeared the patients were given antibiotic or sulfonamides.

Skin infection may occur, especially if trophic disturbances are present. This was not a problem in the present cases, and vitamin A and D ointment proved satisfactory. Danger of burns over anesthetic areas must be emphasized. Cleanliness and good nursing care are essential.

The rehabilitation of the patients, so far as motor paralysis is concerned, is dependent upon the degree of spinal cord damage. In the paralytic stage, the patients should be given radiant heat and massage, and the prevention of contractures and joint stiffening can be accomplished by carrying the affected limbs through a full range of motion twice daily. As soon as voluntary motion begins to return, assistive active exercises can be started and the patient is urged to sit on the side of the bed and

swing the legs. As soon as weight bearing, without tiring is possible, walking training is begun.

With modern treatment to prevent and control bladder infection and early physical rehabilitation procedures, the prognosis of the anterior spinal artery syndrome is definitely better than a decade ago. The degree of permanent crippling will continue to depend on the amount of irreparable damage to the spinal cord.

SUMMARY

1. Six cases of anterior spinal artery syndrome are reported. The onset is sudden or rapid with girdle-like pain followed by loss of perception to pain, touch and temperature, and motor paralysis below the level of the lesion in the spinal cord. Motor paralysis at the level of the lesion is of the lower motor neuron type, but of the upper motor neuron type below.

2. A disturbance of bladder function occurred in all cases with early retention, and in severe cases an uninhibited neurogenic bladder was a residual. Voluntary bladder control was reestablished in a few weeks in most cases.

3. The lesion occurred in the lower cervical spinal cord in two cases and in the mid-thoracic and lower thoracic cord in the remainder. Syphilitic arteritis was the etiologic factor in two cases, arteriosclerosis in three cases, and infection in one case.

4. The differential diagnosis is discussed. Unless there is grossly bloody spinal fluid with or without spinal subarachnoid block, central hemorrhage into the spinal cord cannot be differentiated from anterior spinal artery thrombosis.

5. The prognosis has been improved by modern treatment of the bladder disturbance and by physical rehabilitation procedures.

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Spread of Sensory and Motor Loss After Nerve Injury

Michael Kelly, M.D.

AFTER injury to a nerve trunk, the sensory and motor loss may spread beyond the field supplied by the injured nerve. Early in World War II two such cases were observed, one a battle casualty and the other a wounded civilian. The belief that this was a rare occurence proved incorrect on observation of a larger number of late cases of nerve injury. In some cases excessive sensory loss persisted for years after the injury; in others the records mentioned transient sensory loss or transient paresis of muscles not supplied by the injured nerve.

CASE REPORTS

Case 1.—A bomb wound in July 1941 had fractured the fibula six inches above the ankle and damaged the musculocutaneous nerve. Four months later there was no motor loss, but the skin of the lower leg and the foot was hyperalgesic. The border between normal and abnormally sensitive skin was quite sharp, in front reaching within 6″ of the patella, and running downwards and backwards above the level of the wound to cross tendo achillis three inches above its attachment (figure 1). Recovery was gradual and finally complete.

Case 2.—A soldier sustained a longitudinal incised wound in the upper third of the anterior compartment of the leg. The muscles supplied by the anterior tibial nerve were paralyzed. Five weeks later they were beginning to recover, but sensory loss in the lateral popliteal field was complete. In addition an area of incomplete loss of sensation extended up to the middle of the thigh on its outer side.

Case 3.—A wound of the ulnar side of the palm, which did not involve bones or tendons, was followed by paralysis of the intrinsic muscles supplied by the ulnar nerve, and by sensory loss in the fourth and fifth digits. After two weeks the medial part of flexor profundus digitorum was paralyzed, and the soldier could not flex the terminal joint of his little finger. The branch to this muscle comes from the ulnar nerve near the elbow. Complete recovery occurred within six weeks.

Case 4.—The calf and the posterior aspect of the lower third of the thigh had been wounded by many small fragments of shell. Complete motor and sensory lateral

34 Queen's Road, Melbourne, Australia

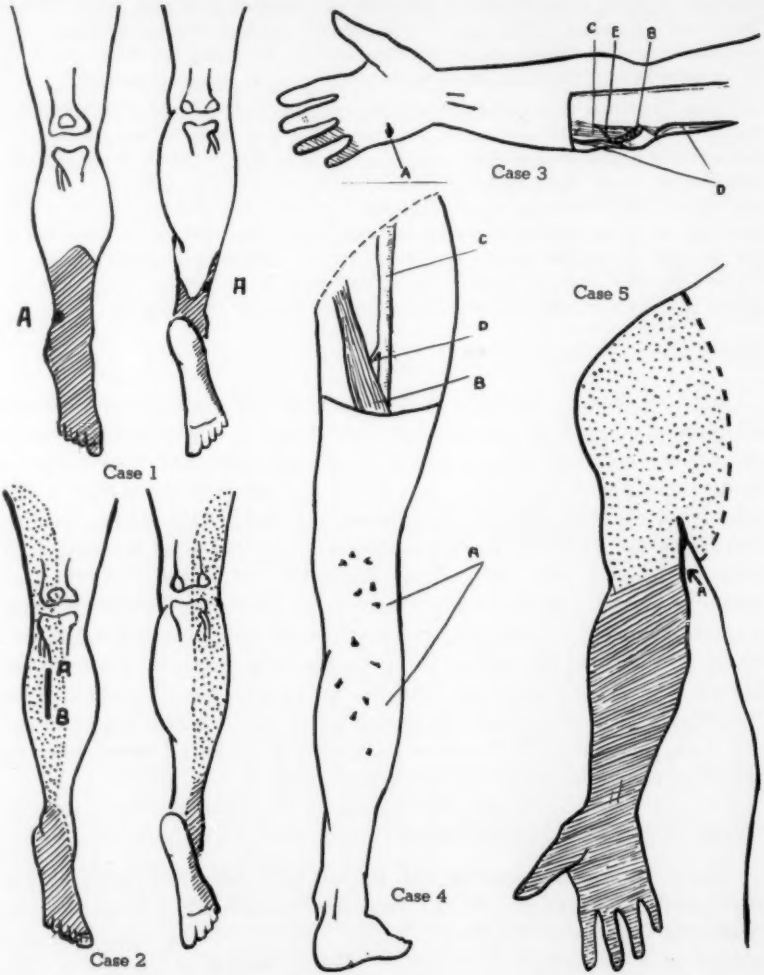

FIG. 1. *Case 1.* Wound of lower leg at A; shaded portion indicates area of hyperalgesia. *Case 2.* Wound from A to B; shaded portion indicates area of complete sensory loss and stippled portion, area of partial sensory loss. *Case 3.* A, wound of palm; B, flexor sublimis tendon (cut); C, flexor profundus; D, ulnar nerve; E, branch of flexor profundus. *Case 4.* Dissection to show nerve supply to biceps femoris; A, multiple wounds of calf and lower thigh; B, biceps femoris; C, sciatic nerve; D, branch to biceps femoris. *Case 5.* A, point of pressure from crutch; shaded portion indicates area of complete sensory loss and stippled portion, partial sensory loss.

popliteal paralysis resulted, and no recovery had occurred four years later. Though there were no wounds in the upper two-thirds of the thigh, the biceps muscle was paralyzed at first but it recovered within three months. The sciatic nerve, when explored in the lower third of the thigh eleven weeks after the injury, appeared normal.

Case 5.—A man aged 50 had fractured his right tibia and fibula. After using crutches for two months he could not extend his wrist and fingers, and the back of his hand felt numb. A month later he could not abduct his arm, and the whole of the arm and shoulder felt numb. Examination revealed paresis of the deltoid and biceps muscles, and of the extensors of the wrist and fingers. Cutaneous sensation was almost totally abolished on the dorsum of the forearm and hand, and diminished on the remainder of the arm and the shoulder region. The area of abnormal sensation extended medially to the mid-clavicular line, and took in the axillary folds. He discarded the crutches and steady recovery took place, the area of dysaesthesia gradually receding.

DISCUSSION

It is not easy to estimate the frequency of this phenomenon, because all observers do not attach the same importance to observations so much at variance with orthodox neurology, and some disregard it as a sign of hysteria. In recent years, however, Kerr[47] has reported the spread of the sensory effects of brachial plexus injuries to the field of the cervical plexus, and Richards[69] observed medial cutaneous involvement in ten out of 26 cases of delayed ulnar palsy. Weir Mitchell[58] and Bowlby[13] in the last century accepted the phenomenon as real, as also have Livingston[53] and several others.[5, 8, 52, 54] Sharpey-Schafer[74] could not have been deceived when, after cutting the digital nerves to his little finger, he noticed that the tip of his ring finger was numb for two weeks. Soca[79] attributed to "traction" the development of a crutch palsy into a plexus lesion (compare Case 5). Learmonth[51] removed a lipoma of the radial nerve, 4 cm. in diameter, which had made the whole arm numb.

SPREAD FROM ULNAR NERVE DAMAGE

Many writers, commencing with Earle,[32] have described the extension of symptoms from injuries of the ulnar nerve (table 1). The field of the median is sometimes involved,[10, 41, 43, 44, 50, 63, 71, 72, 77] and sometimes the median and the radial.[18, 26, 58, 59, 61, 72, 80] Ulnar lesions at the elbow may develop into lesions of the brachial plexus,[70, 88] and sometimes into "ascending neuritis."[7, 9] Spread of sensory loss into the field of the medial cutaneous nerve is comparatively common.[3, 4, 14, 20, 69, 75, 80]

Richards[69] was on the watch for medial cutaneous nerve involvement, but several writers made a chance observation without comment; thus Broca and Mouchet[14] observed diminution of sensibility in the forearm; Shelden[75] recorded "antebrachialis also affected"; Adson[3] recorded

TABLE 1

ADDITIONAL NERVES INVOLVED IN ULNAR NEURITIS FROM VARIOUS CAUSES

Author	*Total Cases*	*Medial Cutaneous*	*Median*	*Multiple Nerves*
Adson	3	1		
Alajouanine and others	1			1
Behague and Turon	1			1
Broca and Mouchet	4	1		
Bennett	1			1
Bernhardt	1		1	
Cotton	7			1
Davidson and Horwitz	2	1		
Duchenne	1			1
Earle	1	1		
Huet	1		1	
Laurence	7		1	
Mitchell	3		1	1
Mouchet	4			1
Neel	5			1
Platt	12		1	
Richards	26	10		
Ruvertoni and others	1		1	
Savariaud	4		2	2
Shelden	22	1		
Singer	36		4	2
Sunderland and Kelly	25	5	1	3
Watson-Jones	13	1		

numbness in the forearm. In 25 cases of delayed ulnar palsy, Sunderland and Kelly[80] saw five instances of spread to the medial cutaneous field and four to the median and radial.

At first sight, the spread of motor and sensory loss appears mysterious and inexplicable. But a simple explanation comes from the simultaneous application of two known facts concerning the nervous system, one pathological and the other morphological: (1) chromatolysis of sensory and motor neurones after injuries to nerves; (2) the branching of fibers in nerve roots and trunks.

CENTRAL EFFECTS OF NERVE INJURIES

"It is often forgotten," wrote Young,[91] "that there may be a very considerable complete central degeneration of many fibers and their cells

after severance of a nerve." Brown-Séquard[15] and Vulpian[86] first studied in animals the central effects of experimental damage to nerves, but the proper study of chromatolysis was delayed until the introduction of Nissl's staining methods. The majority of the cells of the spinal ganglia, however, are small, with naked axis cylinders, and their more intense reactions to trauma are difficult to recognize. Many of them are rapidly invaded by fibroblasts and disappear before chromatolytic changes appear in the larger cells.[34, 62, 65] In rats Ranson[65] found that 54 per cent of the neurones in the second cervical ganglion perished after section of the root distal to the ganglion. The fibroblastic reaction subsided within 60 days, and the surviving neurones moved closer together; the ganglion became smaller than its fellow, but its histological appearance was not very different.

Chromatolysis has been studied also in the large neurones of the anterior horns.[6, 36, 85] After section of the guinea-pig's sciatic nerve 38 per cent of these cells react and 16 per cent to 20 per cent finally perish.[85]

In man, after disease of nerve-roots[16, 21, 48] or after amputation of a limb,[56, 60, 84] there is permanent loss of cells and fibers from the grey matter of the cord and from the spinal ganglia.

FACTORS GOVERNING CHROMATOLYSIS

The intensity of the reaction is influenced by certain known factors:[57]

(1) Violence to the axon. It is less when nerve is cut than when it is avulsed: still less when it is ligated.[57]

(2) Distance of lesion from cell. It is greater in injuries of nerve roots than of trunks.[57]

(3) It is greater in sensory than motor neurones, and especially in small cells of spinal ganglia, whose axons are not medullated.[65]

If the reactions of man resemble those of animals, many neurones will be damaged after a nerve injury. The more intense destruction of sensory neurones explains the greater sensory loss that often follows partial lesions of mixed nerves.

BRANCHING OF FIBERS IN NERVE ROOTS AND TRUNKS

How much do axis-cylinders divide as they run in nerve-roots and nerve-trunks? This question, which is of fundamental importance, has excited little interest among clinical neurologists. Sjoquist[78] mentioned it in his study of the trigeminal nerve; and twice during recent years the branching of fibers has been suggested to explain sensory disorders in man: (1) referred visceral pain,[76] (2) the spread of causalgic pain.[81] There

is abundant information that branching in nerve roots and peripheral nerves is the rule.

NERVE ROOTS

Rudolf Wagner,[87] observing that the distal portion of the sensory root was thicker than the central portion, suggested that the increase might be due to branching of fibers. Many authors later found that medullated fibers were more numerous in trunks than in roots.[11, 19, 22, 35, 39, 73] Fibers were counted proximal and distal to the spinal ganglion, and sometimes the distal excess was as much as 61 per cent.[40] Ranson[64, 66] confirmed these findings, but attributed them at first to experimental error. The excess was due in part to the medullation of the distal prolongations of many ganglion cells whose central prolongations were not medullated.[46]

PERIPHERAL NERVES

In the frog's sciatic nerve, Dunn[29, 30, 31] and Donaldson[23] showed that motor and sensory medullated fibers increased in number in a distal direction. Branching was observed microscopically; sometimes the branches went into different nerves. In man, Ingbert[45] found that 6 per cent to 8 per cent of the medullated sciatic nerve fibers divided in the thigh, and 21 per cent in the branches of the sciatic in the leg.

Branching of fibers is common in the sympathetic trunks of animals,[49] and in the following somatic nerves: motor trigeminal fibers of rabbit;[89] motor nerves of cat;[1, 17, 33] mixed nerves of rat;[37, 38, 82, 83] oculomotor nerves of man and animals;[12, 55] cutaneous nerve of frog;[2] vagus nerve of cat;[46] lingual nerve of cat.[92]

NAKED FIBERS IN SENSORY ROOTS AND TRUNKS

In motor roots naked fibers comprise 5 per cent to 15 per cent,[42] but in sensory roots the proportion may be 75 per cent.[27, 28, 67, 90] In the cutaneous nerves of man it is higher.[25, 68] Naked fibers branch seven times more freely than medullated fibers[24, 68] In peripheral sensory function, therefore, medullated fibers do not play so important a part as the naked fibers, whose profuse branching cannot be followed by ordinary histological methods.

CHROMATOLYSIS OF PARENT CELLS OF BRANCHING AXONS

Sensory fibers, we have seen, branch more freely than motor. Let us suppose that many of the sensory fibers in the ulnar nerve divide and that each sends one branch into the little finger and one into the ring

finger. Damage to a digital nerve of the little finger (as in Sharpey-Schafer's experiment[74]) would put out of action, through chromatolysis, many of the neurones in the first thoracic spinal ganglion. Since, however, many of these neurones send branches into both the ring and little fingers, we should not be surprised if sensation is disturbed on the tip of the ring finger. It will recover as the ganglion cells return to normal. In any given case of nerve injury, the amount of spread of motor and sensory loss depends on the amount of branching of axis cylinders and on the amount of damage to neurones in anterior horn cells and spinal ganglia.

SUMMARY

1. Damage to a peripheral nerve is sometimes followed by spread of sensory and motor loss beyond the field of the injured nerve.

2. In ulnar nerve injuries, extension of sensory loss into the field of the medial cutaneous nerve is not rare.

3. Chromatolysis of neurones, after damage to a nerve, involves sensory more than motor neurones, and especially the small cells of the spinal ganglia whose axons are not medullated.

4. Medullated motor and sensory fibers branch in nerve roots and trunks, and the more numerous naked sensory fibers branch more freely.

5. The spread of motor and sensory loss, therefore, can be explained as the effect of chromatolysis of cells whose axons divide and send branches into two different nerves.

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The researches recently made in animals on the functions of the brain, although of great importance, need to be complemented by similar investigations, or by corresponding pathological alterations, in the human brain. Notwithstanding the general similarity in the conformation of the brain of man and that of the highest animals of the order—primates, special differences of great importance are very apparent. The same remark is true of the Orang and of animals in the scale below him. The brain of man differs still more remarkably from that of the inferior animals, in the extent and variety of its functional manifestations. It is obvious that it is exceedingly desirable to ascertain how far the results of experiment on the brain of animals may be employed to elucidate the functions of the human brain.

—Roberts Bartholow, M.D., in *Experimental Investigations into the Function of the Human Brain*, published in 1874.

The Face-Hand Test as a Diagnostic Sign of Organic Mental Syndrome

Max Fink, M.D.,
Martin Green, M.D. and Morris B. Bender, M.D.

In the course of sensory studies by the method of double simultaneous stimulation, it has been observed that patients with mental changes may show perceptual errors which are not demonstrable by routine single stimulation.[1] When stimuli are simultaneously applied to the cheek and the hand (the face-hand test[2]), patients frequently report only one of the two stimuli, or when reporting the two stimuli mislocalize one to another part of the body or even into space. These changes in perception are seen on repeated trials of the face-hand test and seem to form a consistent part of the syndrome usually labelled "organic mental syndrome" or "organic psychosis."

SUBJECTS

Four hundred patients, who manifested cerebral dysfunction in the form of an organic mental syndrome due to a variety of causes, were studied on the wards of the Bellevue Psychiatric Hospital.* Each patient manifested, to some degree, the following mental changes: (1) impairment of memory, for both recent and remote events; (2) confusion and disorientation for time, space, situation and body image; (3) errors on calculation and general information tests; (4) distractibility, poor attention span, inability to handle more than one situation at a time, concreteness and

*This number represents several series of patients in whom the method of double simultaneous stimulation were applied. It includes all tests of the face and hand by touch, pin prick and combinations of touch and pin prick stimuli, as well as tests of body areas other than the face and the hand.

From the department of neurology and psychiatry, New York University College of Medicine, and the department of neurology and psychiatry, Bellevue Hospital, New York City.

This work was aided in part by a Fellowship from the National Foundation for Infantile Paralysis, and by a research grant from the United States Public Health Service, National Institutes of Health.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1951.

rigidity in thinking; (5) perseveration of speech and behavior; (6) emotional liability and readily elicited "catastrophic" reaction; (7) loss of initiative and interest in the environment and indecent exposure and soiling of the clothing. The clinical diagnoses were varied, including chronic alcoholism, post-traumatic encephalopathy, hypertensive cerebrovascular disease, diffuse arteriosclerotic softening, syphilis of the central nervous system and degenerative diseases, such as Alzheimer's disease, Huntington's chorea or senility.

Observations on the face-hand test in patients with organic brain disease were compared with previously obtained results of similar examinations in normal adults and children and in adult patients with schizophrenia[2]. The normal adults and children, including students, associates and patients in clinics, were without manifest disorder of the nervous system. The schizophrenic adults were patients from the wards of the Bellevue Psychiatric Hospital. No effort was made to group the patients into the various clinical types of schizophrenia.

METHOD

The face-hand test was applied to each of these subjects. During routine physical examination the patient was asked to close his eyes. One cheek and the contralateral hand were simultaneously touched or stroked by the examiner's fingers. The patient was then asked what he had felt. The usual response was, "You touched me here," while pointing to the cheek. After this initial application of the face-hand test, the patient was again asked to close his eyes and the contralateral cheek and hand were similarly stimulated. In the many instances when only one percept was reported, the patient was asked if he had felt anything else. Occasionally the second percept was reported after this question, but more often it was not. Thereafter the tests were applied to the face and hand and to other parts of the body.

RESULTS

In patients with the organic mental syndrome most responses to the initial and subsequent face-hand tests were of four types: (1) a touch on the cheek only, implying no sensation in the hand; (2) a touch on each cheek, implying a mislocalization or displacement of the percept evoked in the hand to the cheek; (3) a touch on the hand only, implying no sensation in the cheek; and (4) correct localization of the percepts evoked in the cheek and hand. Less frequently other responses were noted, as both percepts in the hand, or a percept in the cheek and homolateral hand implying a mislocalization from one hand to the opposite hand. In a few cases the

percept in the hand was mislocalized to a part of the body upon which the hand was resting, out into space, or onto the examiner's body.

The following case illustrates the various responses of patients with an organic mental syndrome.

Case 1:—A 60 year old man was admitted to the psychiatric hospital with a one year history of progressive difficulty in concentration, inability to continue work, mood disturbances, episodes of confusion, forgetfulness and occasional lapses into irrelevant speech. Later, following the death of his wife, he became depressed, cried frequently, and spent many hours talking to himself.

The neurologic examination showed minimal right facial weakness and some gross tremors of the hands. On psychiatric examination the patient answered questions coherently and relevantly. He was euphoric and friendly. There was disorientation for time and place, his memory for both recent and remote events was poor, and confabulation was frequent. Calculation and general information tests were performed poorly. Judgment was poor and there was no insight into his difficulties. When left alone he carried on a conversation with himself, and when presented with a mirror he identified the image as that of his brother and conversed with the image, listening for replies and reporting them to the examiner. In addition, there were difficulties in expression, both verbal and written, with errors in reading, calculation and reporting numbers. He was able to carry out simple commands but made errors in imitating mouth and hand movements. He handled objects clumsily. There was right-left disorientation, and he made errors in naming body parts.

Psychometric examination revealed a severe organic impairment with defects in memory, concentration, abstraction, and concrete verbalization. His performance on the Kohs block test was severely deficient, exhibiting ability to complete only the first two figures.

On sensory examination by the method of single stimulation he could identify and localize pin prick and touch stimuli, except that stimuli applied to the left hand

TABLE 1

Stimulus	*Response*	*Type of Defect*
Right cheek, left hand	Right and left cheek	Displacement
Left cheek, right hand	Right and left cheek	Displacement
Right cheek, right hand	Right cheek, right shoulder (?)	Displacement
Left Cheek, left hand	Left cheek only	Extinction
Right and left hand	Correct	
Right and left cheek	Correct	
Right cheek, left shoulder	Right and left cheek	Displacement
Left cheek, right shoulder	Left cheek, left shoulder	Displacement-allesthesia
Left foot, right hand	Left foot, left hand	Displacement-allesthesia
Left hand, right foot	Right and left foot	Displacement
Right and left hand	Out into space*	Exosomesthesia
Right cheek, right hand	Two percepts right cheek	Displacement
Left cheek, left hand	Left cheek only	Extinction
Right and left cheek	Correct	
Right cheek, left hand	Right and left cheek	Displacement
Left cheek, right hand	Right and left cheek	Displacement

*Patient mislocalized these percepts into space, insisting that the stimulation had not been applied to his body.

were occasionally displaced to the shoulder or the face on the same side. There were no significant differences in temperature, vibration, position sense, and two-point discrimination tests on the two sides of the body. Stereognosis was intact. Examinations by the method of double simultaneous stimulation elicited many defects in cutaneous perception. These were manifest by extinction and displacement of percepts. The errors were persistent despite numerous examinations and over many weeks of study. Table 1 is an extract from the record of the patient's responses to touch stimulation.

Similar errors in localization of percepts were found when continuous and repetitive pin prick, tuning fork and temperature tube stimulations were used. On simultaneous stimulation of the cheek and any other region of the body, the patient correctly localized the percept in the face but seldom perceived correctly, or at all, the other stimulus. This was particularly evident when the cheek and hand were tested, especially a cheek and contralateral hand.

A pneumoencephalogram revealed symmetrically dilated ventricles without displacement. A biopsy of brain tissue removed from the right cerebral hemisphere disclosed a prominence of senile plaques, Alzheimer cells and fatty pigmentation of neurons.

COMMENT

In this case there was no question as to the clinical diagnosis. The presence of defects in perception is not surprising. It is significant that despite the severity of the mental dysfunction the alterations in perception were consistent and patterned. Even though the patient appeared confused he never made errors in perception and localization of stimuli on the face, whereas he frequently erred in the simultaneously stimulated hand. Extinction and displacements from the hand were frequent during many examinations. These perceptual errors were conspicuous by their consistency, orderliness and predictability against a background of apparent mental confusion. These changes can be considered a prominent sign in the organic mental syndrome.

DISCUSSION

Incidence of errors on the face-hand test: Of 156 patients with organic mental syndrome, 91 per cent made errors on the initial trial of the face-hand test using touch stimuli. Subsequent trials revealed a similar high incidence of errors. These errors were in a definite pattern, in which the face percepts were correctly localized, and the hand percepts either not perceived or mislocalized. Displacement of percepts from the hand to the cheek was a prominent feature during the initial few trials of the test. Errors were noted on both sides of the body and occurred on tests applied to cheek and hand on the same side of the body, or on opposite sides. In 87 per cent of the patients errors were apparent through the tenth trial of the test and persisted for many more trials. Repeated testing

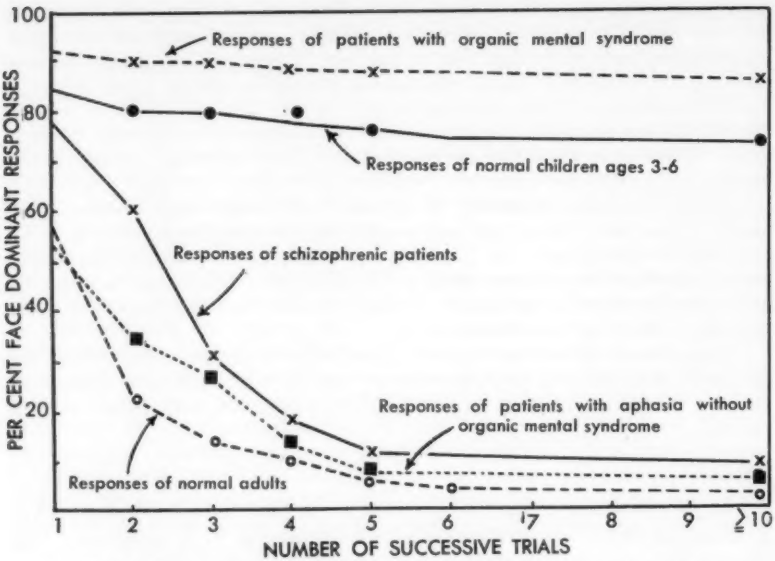

FIG. 1. Responses on multiple trials of the face-hand test to touch stimuli:.

on subsequent days elicited similar errors. It must be emphasized that these patients were able to correctly identify and localize single stimuli applied to the face and hands.

In significant contrast to these observations on patients with organic mental syndrome are the observations on normal and schizophrenic adults.[2] On the initial trial of the face-hand test to touch stimuli, 50 per cent of the normal adults and 75 per cent of the schizophrenic adults failed to report one of the two stimuli. As the test was reapplied, the percentage of error rapidly declined until by the tenth trial of the face-hand test less than 0.5 per cent of the normal adults and less than 3 per cent of the schizophrenic adults still showed omissions or mislocalizations of percepts (figure 1). However, examination of children, age three to six years, with this method again showed a very high incidence of defects on face-hand tests. The curve of responses, as noted in figure 1, is parallel to the curve of responses of the patients with organic mental syndrome. The errors persisted for many trials and were observed in testing over many days. In older children, the curve of responses approached that of the normal adult.

A number of factors were found to influence these responses. Such elements as the type of stimulus, the conditions of the test, the part of

the body stimulated, "set" and "attention" of the patient, the type and severity of the mental changes, and the effect of drugs were considered.

Timing and type of stimulus: In previous studies on normal and schizophrenic adults,[2] simultaneity, similarity and equality in strength of stimuli were emphasized as essential for eliciting these responses. In the patients with mental changes, however, these factors were not as prominent since stimuli of unequal intensity or of different modalities still elicited errors in the tests. Dissimilar stimuli, as application of a touch stimulus to the cheek and a pin prick stimulus to the hand, or stimuli of unequal intensity, as a light touch to the cheek and forceful rubbing in the hand, elicited extinction and displacement of percepts. Similarly, errors in localization were elicited even if stimuli were not simultaneous, i.e. followed one another with a lapse of a moment or two. As previously reported, these errors on unequal, or dissimilar stimulation were not seen in the normal or schizophrenic controls.

Application of the face-hand test using pin prick stimuli elicited the same pattern of responses as with touch stimuli. Eighty per cent of the patients made errors on the initial trial and such errors persisted in 60 per cent for more than ten trials. This incidence of defects is lower, however, than in the series with touch stimulations (table 2). In some of these patients it was possible to alternate touch and pin prick stimuli, and observe extinction and displacement of the touch percepts alternating with correct responses to pin prick stimuli. In a number of the more severely affected patients, extinction and displacement of percepts were also apparent on tests with temperature tubes, tuning forks and repetitive rubbing stimulations.

TABLE 2

INITIAL TRIAL

	Modality	*Total*	*Correct*	*Face Only*	*Face-Face*	*Hand or Hand-Hand*
Organic Mental Syndrome	Touch	156	15	122	14	5
	Pin Prick	50	10	35	3	2
Normal Adult	Touch	160	77	75	3	5
	Pin Prick	68	51	15	2	0
Schizophrenic Adult	Touch	72	24	45	1	2
	Pin Prick	50	36	13	0	1

This factor of the type of stimulus was more prominent in the normal and schizophrenic subjects. Less than 30 per cent of these made errors on the initial trial with pin prick stimuli, and the number of errors declined rapidly until by the tenth trial none of the normal subjects and only one of the schizophrenic subjects still showed errors.

Part of body stimulated: In these sensory studies by double simultaneous stimulation methods, a definite relationship in the perception of cutaneous stimuli between various body parts was apparent. On stimulation of dissimilar body areas with the face as one locus, the stimuli to the cheeks were well localized and identified, while stimuli elsewhere were either not perceived or poorly localized. Combinations of stimuli to the face and trunk, face and foot, face and hand, etc., repeatedly showed face dominance. In contrast, in tests with the hand as one locus, the hand percept was always poorly perceived and poorly localized. This was observed in the initial trials in the normal and schizophrenic adults, but was more apparent in multiple trials in patients with organic mental changes. By repeatedly testing various combinations of other body areas, a gradient of the sensory relationships of these areas has been established. Because the face and hand regions represented the extremes in the pattern of responses, these two regions were selected as the basis of most of the tests. Therefore, this method of examination was named the face-hand test.

The errors in these examinations were apparent in tests of both sides of the body without any manifest preference. In patients with hemiplegia of recent onset and associated mental changes, extinction and displacement of percepts were apparent bilaterally, but were more prominent and more persistent on the involved side of the body. In patients with long-standing hemiplegia in whom the mental syndrome was no longer apparent, the defects were limited to the involved half side of the body.[3]

The factor of mental set: The mental set or attitude often influenced the perceptual response. Once the normal adult was examined by the method of double simultaneous stimulation, subsequent tests failed to elicit a repetition of the errors which occurred on the initial face-hand test. It was as if these subjects had "learned" the set of "two-ness." Moreover, when normal subjects were tested with face-face stimuli, the responses were correct, and then all subsequent face-hand tests were also correct. When face-face tests were interposed among trials of the face-hand test in the patients with mental changes, they continued to make errors on tests of face and hand, even though they were correct on the face-face trial. Such errors persisted for days. Evidently mental set and learning did not alter the pattern of response.

The factor of attention: It is well known that attention can influence perception.[2, 4] In a series of 30 normal adults who were told that two stimuli were to be applied, none made errors on the initial trial of the face-hand test. However, patients with severe mental changes, who were

told either before the initial trial or on subsequent trials that there would be two stimuli, still showed extinction and displacement of percepts. It was possible to have the patient, with eyes open, observe the application of two stimuli and report them correctly. Then, with eyes closed, and the stimuli applied to the same or homologous areas, the patient would report the stimuli incorrectly.

The effect of fatigue on the performance of the patient has already been mentioned. It is possible to increase the errors of the patient by administering the stimuli more frequently, or by making him aware of his errors and thereby increasing his anxiety. With mounting anxiety, errors increase until culminated by a catastrophic reaction and withdrawal from the examination. A similar effect of anxiety on performance was manifest in the normal subjects. The adults with manifest severe anxiety required more trials of the face-hand test to perceive the percepts correctly than adults without manifest anxiety.

Degree of mental changes: We found a definite relationship between the severity of the mental changes and the frequency of errors in perception in the patients with an organic mental syndrome. The patients varied in their mental status from mild memory disturbances and alteration in intellectual ability, to severe psychomotor retardation, amnesia, aphasia and somnolence. The responses to the face-hand test varied from occasional extinction of percepts seen in the mild cases, to consistent, bilateral displacement of percepts to other parts of the body, the examiner's body, or into space in the subjects more severely affected. In a number of patients with severe head trauma or following cerebral surgery, the progressive improvement in mental functioning was accompanied by a change in response to repeated trials of the face-hand test. The responses changed from bilateral displacement and allesthesia when damage was most severe, to extinction in decreasing frequency and finally consistently correct responses as the subject improved.

Perceptual errors were greatest in subjects in whom nervous system dysfunction was acute in its course with rapid onset and short duration. Patients with severe head trauma, infections of the nervous system, vascular accidents and neoplasms were more likely to show extensive changes on double simultaneous stimulation than patients with chronic alcoholism or senility. It was in these last two groups that there were a number of subjects with organic mental changes who consistently perceived the two stimuli of the face-hand test correctly on the initial and on multiple trials.

Type of mental defect: There was no obvious correlation of the frequency of errors in the face-hand test with any single symptom of the

organic mental syndrome as in patterns of thinking, spatial or body orientation, memory or calculation. Errors in perception were most apparent when disturbances in function were most widespread.

A good correlation existed, however, between the patient's alertness and the responses on the face-hand test. In patients who were apathetic or lethargic, errors on double simultaneous stimulation were most prominent. This was apparent in many subjects who made errors occasionally during the initial trials of the face-hand test, but in whom errors became more frequent and changed from extinction to displacement responses as the examination continued. Similarly, in testing patients with fluctuating states of consciousness, there was a good correlation between the degree of alertness and the responses on multiple trials of the face-hand test.

Some of the patients were unable to carry out tasks which had two different aspects. But despite this inability to do two things at once they were able to perceive the two stimuli applied to the sides of the face. Therefore, it could not be said that the inability to correctly perceive one of the two stimuli applied to the face and hand was due to a defect in the ability to perform a task with two different components.

The factor of aphasia: Aphasia is sometimes considered a defect in mentation. Such a defect, where severe or associated with mental changes characteristic of the organic mental syndrome, yields a picture of the patient as confused. For instance, a patient with aphasia may also have a loss of memory and an inability to recall or recognize situations even after they are described to him. In order to determine whether aphasia per se will produce errors in the face-hand test, aphasic patients, with or without such mental changes, were studied. Patients with aphasia but without mental changes did not make errors on the face-hand test, while patients with aphasia and mental changes made repeated and consistent errors on multiple trials of the test (figure 1).

Organic mental syndrome with normal responses on the face-hand test: As already noted, not all patients with an organic mental syndrome make errors in tests by the method of double simultaneous stimulation. In a series of 271 patients in whom various combinations of these tests were applied, there were 228 patients who made errors and 43 patients who gave correct responses on initial trials. Of these latter, however, there were 22 who made errors after the initial trial. The remaining 21 were correct throughout multiple trials. Of the 228 patients who made errors on the initial trial there were 28 who were subsequently correct and yielded responses similar to the normal as carried out in one series of tests. In summary, it was found that 49 of the 271 patients with mental changes

yielded normal reactions. All of these 49 patients had an organic mental syndrome but in general the mental changes were not severe. Memory loss was spotty and the degree of orientation varied, Apathy was seldom marked. There were fluctuations in performances. At times there were long intervals, minutes to hours, during which the patient showed no apparent mental changes. Examinations during those symptom-free intervals showed the face-hand test to be normal. In several instances it was learned that the defects in memory or indifference in answering questions pertaining to orientation were due to an emotional depression or to a phlegmatic premorbid personality. Their organic mental syndrome was only apparent and not real. There were, however, 11 patients with severe mental changes who reported correct responses on repeated face-hand tests.

Effect of drugs: From the foregoing studies it is clear that patients with organic mental syndrome make errors in perception in double simultaneous stimulation tests. Consequently it was thought that the mental changes induced by drugs should yield similar errors. To test this theory, normal adults were subjected to intravenous injections of 7 to 10 ml. of a 5 per cent solution of sodium Amytal administered slowly. This drug produced the usual nystagmus, dysarthric speech and drowsiness. In addition, normal adults, who made no errors on the face-hand test prior to the injection, now made consistent bilateral errors. Within 5 minutes after the injection errors were apparent on many repeated trials of the test and these persisted during the period the drug action was effective. The more drowsy or intoxicated the subject became the greater the tendency to make errors in perception. At the onset, displacements of hand percepts were frequent, but as the drug effect diminished, displacements diminished and extinction of hand percepts became prominent—only to disappear as the subject became more alert. Similar effects have been observed in the patients with a mild mental syndrome. Where only extinction of hand percepts was apparent prior to the Amytal injection, displacement of percepts became frequent and persisted for the duration of the examination. The effect of the drug persisted for longer periods in patients with organic mental changes than in normal adults, so that displacement of percepts was manifest hours after the injection in the patient group.

Similar observations on the effect of anesthetics on central nervous system function have been made in a study of normal adults subjected to varying periods of anesthesia.[5] These subjects with no demonstrable disease of the brain, who made no errors on double simultaneous stimulation tests prior to anesthesia, manifested extinction and displacement of

percepts in either hand on multiple trials of the face-hand test during recovery from anesthesia. When these subjects regained consciousness from a general anesthetic, they were disoriented and confused. There was a manifest correlation between the duration of the perceptual errors and the period of confusion, lethargy and apathy that followed the anesthetic administration.

Effect of convulsions: During post-convulsive states patients frequently show confusion and other symptoms of the organic mental syndrome. Since persistent errors on the face-hand test were found in patients with mental changes due to disease of the brain or due to drug intoxication, it was thought that any one who has an organic mental syndrome, of whatever cause, should show these errors. For this reason, groups of patients were studied in whom convulsion were induced electrically for treatment of depressions. Patients who were given intravenous barbiturate preliminary to electric stimulation were not included in this group.

It was found that if the post-convulsive confusional state was severe, these patients showed a high incidence of errors on the face-hand test. As soon as the confusional state cleared, the incidence of errors in the face-hand test decreased.

Value of the face-hand test as a diagnostic sign: In order to determine the value of the face-hand test as a diagnostic sign of severe mental changes, a series of patients were examined in the admission ward of Bellevue Psychiatric Hospital. This examination was carried out by simultaneous stimulation of the face and hand. Each patient was given a series of 10 tests. No history was taken nor were other clues used to make a diagnosis. Using this method it was found that in all cases in which the face-hand test showed errors on repeated trials, subsequent psychiatric examinations disclosed the presence of an organic mental syndrome.

CONCLUSIONS

From the foregoing observations it is apparent that subjects with the organic mental syndrome showed persistent errors on face-hand tests. It is significant, however, that the same confused and disoriented patients did not err in a haphazard fashion. An analysis of their responses based on numerous tests showed that the errors were made in a predictable pattern. There were consistent errors in the hand percepts, whereas there were very few errors in response to the simultaneous stimulations applied to the face. Another significant point is that this pattern was found not only in patients with cerebral dysfunction, whether it was due to structural or chemical changes in the brain, but also in normal children. This was found in children in whom the brain was not altered in any manner. The latter

observation indicates that this pattern is not the result of disease of the brain, and conversely, that it is inherently organized. Moreover, it indicates that this pattern is acquired early in life.

No explanation is offered as to why these patterns are so organized, namely, face dominance and hand "extinction." The rostral dominance theory proposed by Cohn[6] cannot be supported by these observations, inasmuch as it was found that the foot dominates over the hand. This fact automatically precludes the factor of rostral dominance. Moreover, the authors do not wish to agree or disagree with the well known theories proposed by Goldstein.[7]

Still another point is that reactions of the child are similar to those of the senile individual with mental changes. One might draw an analogy to the Babinski sign, which is considered normal in the developing infant and abnormal in the adult. From this analogy, it might be inferred that the presence of persistent errors on the face-hand test in the adult indicates a regression to the infantile level. However, we do not wish to convey the idea that we concur with such a theory.

Finally, it might be concluded that what is seen in patients with disease are normal patterns of function which appear to be grossly exaggerated. As noted, repeated errors on face-hand tests may be found in the normal adult under certain conditions, particularly when there is altered brain function. Based on this hypothesis it is felt that a good deal of information about normal function can be obtained from patients with dysfunction as a result of altered structure.

Aside from the theoretical considerations it must be concluded that the face-hand test has clinical value. It is a diagnostic sign of the organic mental syndrome. The persistence of errors on face-hand tests in an adult strongly suggest an organic mental syndrome.

SUMMARY

Patients with an organic mental syndrome make persistent errors in tests by double simultaneous stimulation of the face and hand. The errors are usually made in the hand. These errors are made on multiple trials of the face-hand test and on subsequent examinations on repeated days. The normal and the schizophrenic adults, however, do not make persistent errors. This difference in response between these groups is so striking as to have diagnostic value.

Errors of extinction and/or displacement on multiple trials of the face-hand test by touch stimulation are indicative of the organic mental syndrome. In a series of patients examined in the admitting room of the Bellevue Psychiatric Hospital, these tests were applied to patients as the

first questions of the interview. The diagnosis of an organic mental syndrome was confirmed by subsequent interview in every case. The significance of these findings is discussed.

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In order to conceive a clear idea of the pathology, we have only to imagine the physiological phenomena, already noticed, assuming a pathological character. Now, the force of these phenomena may be augmented, diminished, or annihilated.

In regard to the cerebral functions, we have, in the sentient nerves, pains or insensibility; in the cerebrum itself erroneous perceptions, judgments, and colitions, or delirium; or a total deficiency of these faculties, or come; in the motor nerves continual voluntary actions; or paralysis.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

Use of Benadryl for Symptomatic Relief of "Thalamic Pain"

Ralph W. Barris, M.D., Ph.D.

DEJERINE and Roussy in 1906 and 1907[1, 2] first called attention to a clinical entity since referred to as the "thalamic syndrome." Usually caused by a vascular lesion, most frequently either occlusion or rupture of one of the thalamo-geniculate branches of the posterior cerebral artery, such a syndrome may be partial or complete with a resultant set of signs and symptoms constituting a characteristic group. There is a diminution of cutaneous sensibility without complete anesthesia on the opposite half of the body, involving limbs and trunk, with the face as a rule spared. In reality, the threshold for tactile, pain and temperature sensations appears elevated, and the quality of sensory impression is abnormal, being disagreeable or unpleasant. It is variously described by patients as "hot," "stinging," "tingling," "icy," "burning," "pricking," "tickling," "stabbing," "tearing," "like a vise," "tearing the skin," "scratchy," and by other common adjectives denoting an unpleasant feeling. There is usually an associated reduction of deep sensibility involving sense of passive movement, deep pressure and vibratory sensibility. Such activities as lying on the affected side in bed, being bathed or dressed, being lifted into or out of bed or wheel chair, or the excessive pressure of bed clothes are all apt to cause the patient excessive discomfort to which he responds at times as if in agonizing pain. This over-reactivity, or hyperpathia, or hyperaffectivity, greatly interferes with the early ambulation and application of such physiotherapeutic measures as massage and passive motion of

From the department of medicine (neurology), School of Medicine, University of California at Los Angeles, and neurology section of the medical service, Wadsworth Hospital, Veterans Administration, Los Angeles, California.

Reviewed in the Veterans Administration for publication with the approval of the chief medical director. The statements and conclusions published by the authors are the results of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1951.

TABLE 1

NEUROLOGICAL SIGNS AND SYMPTOMS

PATIENT	AGE	NO. DAYS between Onset of Symptoms and Initiation of Benadryl Therapy	HEMIPLEGIA (Spastic)	SENSORY THRESHOLD									HYPERPATHIA					PAIN SPONTANEOUS	
				POSITION SENSE	DYSTER-EOGNOSIS	VIBRATORY SENSE	TWO POINT DISCRIM-INATION	DEEP PAIN SENSE	LIGHT TOUCH (Cotton)	PAIN (Pin Prick)	TEMPERA-TURE (Heat)	TEMPERA-TURE (Cold)	COLD	HEAT	PAIN (Pin Prick)	PAIN (Deep	LIGHT TOUCH (Cotton)	ARM	LEG
O.H.	57	121	Rt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+ +	+	+	+ +	+	+ +	+ +
J.M.	49	208	Rt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+ +	+	+	+ +	N	+ +	+
L.M.	58	359	Lt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+	+	+	+ +	N	+ +	+ +
E.J.	54	940	Lt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+ +	+ +	+ +	+ +	+ +	+ +	+ +
W.N.	54	20	Lt	↑	↑	N	↑	↑	N	↑	↑	↑	+ +	+	+	+ +	+	+ +	0
F.D.	73	26	Lt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+	+	N	+ +	N	+ +	+
F.G.	51	1340	Lt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+	+	+	+ +	N	+ +	0
W.R.	63	371	Lt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+ +	+	+	+	+ +	+ +	+
C.N.	49	131	Rt	↑	↑	↑	?	↑	N	↑	↑	↑	+	N	+	+	+	+ +	+ +
C.S.	46	84	Lt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+	N	+	+ +	+	+	+
E.T.	60	533	Rt	↑	↑	N	↑	↑	↑	↑	↑	↑	+	+	+ +	+	N	+ +	0
J.B.	47	81	Lt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+ +	+	+ +	+	+	+	0
R.H.	61	213	Lt	↑	↑	N	↑	↑	↑	↑	↑	↑	+ +	+	+	+	+ +	+ +	+ +
G.H.	54	71	Lt	↑	↑	N	↑	↑	↑	↑	↑	↑	+ +	+	+	+ +	+	+ +	+
C.P.	56	921	Lt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+	N	+	+	N	+	0
E.W.	60	54	Rt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+ +	+	+ +	+ +	+	+ +	+
J.W.	69	19	Rt	↑	↑	↑	↑	↑	↑	↑	↑	↑	+	N	N	+ +	+	+ +	0

the associated hemiplegic extremities, and greatly prolongs the time between the onset of associated hemiplegia and the application of these more specific physical rehabilitation measures such as parallel bar walking exercises, weight and pulley activities, and muscle-stretching maneuvers. Delay in the application of these measures, following excessively long periods of semi-invalidism, often leads to the more seriour sequelae of ankyolsis of the joints of the affected extremities, muscle-tendon contractures, and excessive disuse atrophy of the associated muscles, thus greatly exaggerating the disability inherent in the associated spastic hemiplegic extremities.

In addition to the elevated threshold for cutaneous stimuli on the hemiplegic side of the body, along with the hyperpathia, there as a rule coexists in the "thalamic syndrome" the additional symptom of "spontaneous pain," affecting either the arm or leg or both, variously described by the patient as "boring," "aching," "crushing," or by other adjective to denote its especially agonizing character. This spontaneous pain may become almost unbearable, the patient noting at times a tendency for paroxysmal type of exaggeration. It is not influenced by cutaneous stimulation, but in the present series our attention has been called to the marked exaggeration of this pain on passive manipulation of the extremities, especially if the arm is protracted or elevated at the shoulder, or if the hip is flexed or abducted at the thigh. This spontaneous type of pain is further characterized by its sudden exaggeration at some point of the manipulative procedure with painful reaction which appears to be agonizing to the patient and variously described as "like on the rack," "like my arm (or leg) is being twisted off," and so forth.

Such analgesics as aspirin, codeine, and at times even morphine are usually of little value in giving relief to this spontaneous pain, and the patient often lies in bed, protecting his hemiplegic arm from any motion or handling by covering the hand and wrist with his normal hand or arm. He becomes an especially difficult problem for nursing care and active measures employed in physical rehabilitation of the hemiplegic patient.

In the course of observations of the role of various drugs employed for the reduction of spasticity, Benadryl (B-dimethylaminoethyl benzhydryl ether hydrochloride) was employed experimentally, and the accidental observation made of its beneficial influence on the hyperpathia and spontaneous pain of a hemiplegic patient with other clinical findings conforming to the clinical entity of "thalamic syndrome." Accordingly, a study was undertaken to determine the possible beneficial influence of this drug in other selected cases, all conforming to the clinical definition of this entity.

OBSERVATIONS

A total of 17 patients were selected ranging in age between 46 and 69 years, in whom the "thalamic syndrome" had been existent for periods ranging between 20 and 1340 days, before drug therapy. Oral daily dosages of Benadryl, 400 to 600 mg. in divided doses at mealtime and bedtime, were given to each patient. Daily observations for the first week and weekly observations thereafter were recorded and graded as poor, fair, good, or excellent, depending entirely on the subjective impression gained by the examiner on questioning and examining the patients. Placebos were introduced after two weeks at the termination of active Benadryl therapy, as a method of establishing control observations.

As summarized in table 1, all patients conformed to the clinical syndrome above described as "thalamic syndrome." In table 2, the results of therapy in each of the 17 cases are tabulated. Objectively, the degree of hyperpathia was determined by routine standard testing methods for the responses to heat, cold, light touch, deep pressure and pin prick (pain). The subjective response of the patient and his comparative estimate of his discomfort were taken as approximate criteria in determining the degree of improvement, if any, on drug therapy and noted as fair, good, or excellent. The verbal reports of nursing personnel, the patient, physiotherapists

TABLE 2
RESULTS OF THERAPY
(B-Dimethylaminoethyl benzhydryl ether hydrochloride)

Patient	*Average Daily Dosage (Oral)*	*Number of Days Under Treatment*	*Effect on Hyperpathia*	*Effect on "Spontaneous Pain"*	*Amenability to Rehabilitation Procedures*
O.H.	600	52	Excellent	Good	Excellent
J.M.	400	38	Good	Good	Good
L.M.	400	81	Excellent	Excellent	Excellent
E.J.	400	74	Excellent	Excellent	Excellent
W.N.	400	61	Good	Good	Good
F.D.	600	43	Good	Fair	Good
F.G.	600	71	Fair	Excellent	Good
W.R.	400	62	Excellent	Excellent	Excellent
C.N.	600	84	Good	Good	Good
C.S.	400	42	Good	Excellent	Good
E.T.	600	33	Fair	Good	Good
J.B.	400	24	Good	Good	Good
R.H.	600	78	Fair	Poor	Fair
G.H.	400	62	Excellent	Excellent	Excellent
C.P.	400	38	Good	Good	Good
E.W.	400	28	Good	Fair	Fair
J.W.	600	37	Fair	Good	Good

and attendants were utilized in evaluating the improvement in the patient's tolerance for being clothed, bathed, placed in wheel chairs or in bed, or in being manipulated during massage of skin and muscles, or in the application of more precise physiotherapeutic exercises. The tolerance for maximal passive movement of joints and its relationship to preexistent intolerance of this procedure was noted and recorded, and the subjective improvement in spontaneous pain evaluated and rated as poor, fair, good or excellent. In all, there were five patients who had resisted all forms of physiotherapy, preferring to lie in bed, protecting their hemiplegic and hyperpathic extremities, who within two or three days after the inauguration of Benadryl therapy, were able to sit in a wheel chair, to better tolerate passive massage and manipulation, and who eventually were able to complete an active course of advanced rehabilitative procedures, thus becoming ambulatory and relatively self-sufficient in the course of several weeks. All showed an increased tolerance to otherwise unpleasant stimuli, and as recorded in table 2 the results were described as excellent in five, good in ten, and as fair in two cases.

DISCUSSION

It is felt that Benadryl in relatively high dosages (400-600 mg. daily), is of value in reducing the degree of hyperpathia and spontaneous pain in patients whose signs and symptoms conform to the "thalamic syndrome." In no case was there a complete alleviation of all discomfort associated with the hyperpathia, and in three cases the drug in dosages of 600 mg. daily produced side effects described by the patients as "dizziness," "sleepiness," and in two cases as nausea. In these three cases, the drug was discontinued temporarily and after several days, readministered with a total dosage of 400 mg. daily. In one of these, dizziness was again noted and the drug permanently discontinued.

In the present state of our knowledge, the physiologic basis of "thalamic pain" remains unsettled. Whether due to thalamic over-reactivity due to interruption of inhibitory corticothalamic pathways as suggested by Head and Holmes,[3] or whether this phenomenon of hyperpathia and spontaneous pain is due to the ascending sensory impulses being "short circuited" along phylogenetically older pathways through the thalamus following interruption of the corticothalamic projections as suggested by Dusser de Barenne[4], or whether due to a local irritation of spinothalamic fibers at the site of their termination in the thalamus as suggested by Dejerine[1] cannot be determined. Accordingly, little can be concluded as to the pharmacologic site of action or role of Benadryl in ameliorating the discomfort associated with the thalamic syndrome.

SUMMARY AND CONCLUSIONS

In a series of 17 cases with thalamic syndrome, Benadryl in oral daily dosages ranging between 400 mg. and 600 mg. was of value in ameliorating the symptoms of hyperpathia and spontaneous pain, with consequent acceleration of rehabilitation.

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Nor is a knowledge of the structure and functions, the anatomy and physiology, of the nervous system, sufficient alone, for the full comprehension of the diseases of this system. The nervous system does not exercise its functions uninfluenced by the other systems of the animal economy or by the general system as a whole. The reciprocal influence of these, and the nervous system, must be clearly understood before our view of the subject can be said to be satisfactory.

Indeed, the entire economy of the human frame, although constituted by various systems, is one and indivisible; and it is impossible that one of these systems should be morbidly affected without the participation of the rest. In order to accommodate this difficult and complicated subject to our limited undersanding, it has been found necessary, however, in the pursuit of medical science, to proceed analytically, and to imagine the different systems of which the whole animal economy is composed, to be separated so as to admit of distinct examination; and we speak of the nervous, the circulatory, the respiratory, the digestive, the urinary, the uterine systems, &c. as distinct objects of inquiry. We are compelled, however, afterwards, to review the subject synthetically, and to consider the influence of one or more of these systems, or of the general system upon the other systems, respectively.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

Neurology

Clinical Pathological Conference

From the Department of Psychiatry and Neurology,
University of Southern California

Presented by
J. M. Nielsen, M.D. and J. J. Foster, M.D.

Man with long history of headaches but minimal objective signs, studied 17 months under competent observation before surgery. Large astroblastoma. Death. Autopsy.

W. L., a white hat blocker aged 49, was admitted to the hospital April 10, 1950 with a complaint of sensory left-sided seizures over a period of three years. When the attacks began in 1947 they were confined to the left upper limb and remained so limited for two years. In 1949 the lower limb also became involved. Except for one episode in 1947 in which the patient fell unconscious while shaving without known convulsion he remained conscious in all attacks. As to frequency, the patient had about 25 a day for some months. As they decreased in frequency to about one a week, the attacks simultaneously became painful but the pain was restricted to the left ulnar area of the wrist.

The character of the attacks was quite unusual. The patient felt that the left upper limb was extended before him horizontally but when he looked at it he saw that it remained by his side. He thought in retrospect that an attack lasted two to three minutes. During and after the attack the limb was completely paralyzed and flail-like and remained so for as long as seven minutes, though usually for less than a minute. When the lower limb was involved he dragged his foot although he was able to walk.

Past history revealed that in 1935 the patient had had a penile sore diagnosed as syphilitic, followed by 14 months of intravenous and intramuscular injections. His spinal fluid serology was always negative. In 1944 he developed hyperthyroidism with dysphagia and a loss of weight of 20 pounds. His thyroid gland was then removed. In 1948 he had an appendectomy. There had been no prior cerebral injury. Family history was negative except that he had a brother who was a deaf-mute.

Physical examination at hospital admission showed a well developed, fairly well nourished man of 49 years who did not appear ill. Blood pressure was 140/80, pulse 81 per minute. Neurological examination showed the cranial nerves to be entirely normal, with no evidence whatever of increased intracranial pressure. Re-

flexes were normal except for a slight increase in the left biceps. There were no pathologic reflexes present. A question was raised of impairment of sense of position on the left. The clear spinal fluid was under pressure of 140 mm. of water and the total protein content was 30 mg. per cent. Roentgenograms of the skull revealed no abnormality.

The patient was studied for about six weeks before a right internal carotid angiogram was performed on May 25. Filling of only the proximal portion of the right anterior cerebral artery was obtained. There was no lateral shifting and the general vascular pattern was normal. After this time he had no further headaches. On June 15 a pneumoencephalogram showed the right lateral ventricle to be slightly larger than the left. The right lateral and posterior horns were slightly lower than the left.

Psychiatric examination revealed some loss of memory and auditory hallucinations, and since the patient was tense and anxious he was considered psychoneurotic and depressed. Early schizophrenia was suspected. He was discharged July 17, 1950 with the diagnosis entirely unsettled.

SUBSEQUENT DEVELOPMENTS

On January 27, 1951 the patient was driving his car when his left upper limb began to jerk. His wife related that the patient said, "Look at my hand jerk," and he then lost consciousness, convulsed and bit his tongue. He remained unconscious about half an hour and was confused for two hours. Treated at an emergency hospital, he was given a prescription for Dilantin. His headaches, which had disappeared after the angiogram, now returned. In addition he also suffered from radicular pains referable to the D-6 segment on the left, aggravated by flexion of the spine but not by coughing or sneezing.

He was readmitted to the hospital February 5, 1951. The general physical condition was unchanged but neurologic signs had developed. The physiological optic cups had disappeared and there was generalized hyperemia of the fundi. The deep reflexes were exaggerated throughout, though there was no lateralizing difference and pathological toe signs had not appeared. Roentgenograms of the skull and spine showed only a 50 per cent compression deformity of the D-6 vertebra. Spinal puncture gave clear fluid under a pressure of 245 mm., falling to 200 with better relaxation. The total protein content had now risen to 50 mg. per cent and two white cells per cu. mm. were found. Seen by the senior author at this point, the patient presented all that is given above but a positive Oppenheim reflex on the left was also elicited. A diagnosis was made of a lesion "parasagittally in the posterior portion of the falx near the splenium of the corpus callosum." Exploration was advised. The neurosurgical department, however, in view of the recent and inconclusive angiograms and pneumoencephalograms decided to have psychological studies and await developments.

The psychologist's report April 6, 1951 indicated that the patient was of good intellect but hysterical in spite of the obvious organic component. The patient was followed in the out-patient department as a "brain tumor suspect."

About September 1, 1951 the patient ceased work because of severe headache centering in the right occipital and suboccipital region, extending into the right temporal area. The pains were sharp and throbbing and described as unbearable. Change of position, any vibration such as from the refrigerator, and any noise aggravated the pain. In addition, much nausea and vomiting developed, unassociated with meals. He lost 20 pounds of weight and he hiccoughed. He saw another physician, who found a white blood count of 14,000 per cu. mm. and changed the treatment from anticonvulsants to Streptomycin and penicillin. The white count was reduced to 9,000 cu. mm. but progressive lethargy developed.

He was readmitted to the hospital September 19, 1951. Physical examination showed a well developed but poorly nourished man of 49 years who appeared chronically ill. During the examination he periodically clutched his occipital region

in severe pain. His skin was pale. As he walked he appeared lethargic, weak and exhausted. Blood pressure was 135/78, pulse rate 90 per minute. Neurologic examination showed sense of smell and visual fields to be normal. The optic cup was absent and the margins indistinct on the right, distended veins and slight choking on the left. There was bilateral ptosis of the upper lids. The right pupil was 2½ mm. and the left 2 mm. in size; both reacted to light and on convergence. Extraocular movements were normal. The tongue deviated to the left on protrusion. Other cranial nerves were normal. The deep reflexes were all greater than normal on the left, normal on the right. On the other hand, the abdominals were absent on the left, present on the right. Hoffman reflex was present on the left. Babinski and Chaddock reflexes were equivocal bilaterally. Sense of position was impaired in the left extremities, normal on the right. Pain and temperature perception was unimpaired but astereognosis was present on the left side. There was generalized weakness but no lateralizing weakness.

Laboratory work showed the serology, both blood and spinal fluid, to be negative for syphilis. The blood count showed 4,800,000 red cells per cu. mm., 13.5 Gm. hemoglobin per 100 cc., 12,300 white cells per cu. mm., 70 per cent polymorphonuclears, 26 per cent lymphocytes, 2 per cent eosinophiles, and 2 per cent basophiles. Sedimentation rate was reported as only 2 per cent. The crystal clear spinal fluid was under a pressure of 320 mm. but fell to 200 mm. with better relaxation. There was a slight increase in globulin content but a total protein content of 132 mg. per 100 cc. There were no cells. Sugar was 116 mg. per cent and chlorides 730 mg. per cent.

Roentgenograms of the skull showed a 3 mm. shift of the pineal shadow to the left, a normal sella with some calcification of the petroclinoid ligament. A roentgenogram of the chest showed normal conditions. An electroencephalogram on September 20, 1951 showed phase reversal over the right temporal area constantly. Slow waves were more pronounced on the right than on the left. With monopolar recording a vertex sagittal electrode showed relative suppression of all activity and with bipolar leads a definite suppression of activity in the right vertex-to-right-parietal lead. Pressure was considered to be present and the right fronto-temporal cortex appeared to be most severely affected. The area of relative silence at the vertex and extending to the right parietal electrode suggested the presence of a massive, cortex-destroying, space-occupying lesion, parasagittally placed in the right parietal area.

COURSE IN THE HOSPITAL

The patient was seen by the neurosurgical service and a ventriculogram was scheduled. However, at about 6:00 a.m. on September 21, 1951, the patient became somnolent and slowly passed into a stuporous state. He made withdrawal responses to noxious stimuli, but no other form of arousal could be elicited. There was a divergent strabismus. The pupils were round and equal and reacted sluggishly to light. There was still "early" but definite blurring of the nasal margin of the right optic disk and about one diopter of papilledema on the left. The remainder of the cranial nerves could not be evaluated. The deep tendon reflexes were pathologically hyperactive throughout but much more so on the left. All toe signs were strongly positive bilaterally. The superficial abdominal reflexes were absent. The old roentgenograms were re-evaluated. The angiograms revealed an area of "cotton-wool" increased density in the right parietal area, which was at least suggestively abnormal. Inspection of the pneumoencephalogram elicited no additional information.

After transfer to the neurosurgical service the patient regained consciousness and spoke rationally. A right parietal occipital craniotomy was performed at 1:00 a.m. on September 22, 1951. A large beefy-red tumor was exposed and the borders appeared to be sharply demarcated. The tumor was apparently removed in toto. It appeared that removal of the tumor undermined a portion of the motor leg area and that inferiorly at least a part of

the superior segment of the optic radiation had probably been sacrificed.

PATHOLOGICAL REPORT

The specimen was examined by Dr. J. Sloan Berryman. His report was as follows: "The tumor weighs 127 Gm. with the cortex attached; it measures 5x8x7cm. and the consistency is uniform throughout. On section the tumor is beefy red and of soft consistency; there is a high degree of vascularity. There are no areas of necrosis or cystic spaces; microscopic H. & E. sections disclose a glioma of relatively high degree of cellularity and fairly uniform appearance; the tumor cells identified include fibrillary astrocytes, protoplasmic astrocytes, astroblasts, spongioblasts, and oligodendrocytes. There are great numbers of capillaries and small venules present. No areas of necrosis are seen. Many of the tumor cells are hyperchromatic; Occasional mitotic figures are found. Diagnosis: Astroblastoma."

DISCUSSION

Reconstruction of the history of this case gives the following abbreviated chronological account:

The man, with a history of syphilis many years before, began to have attacks of sensory delusion of movement of the left upper limb at the age of 45. This was then an irritative phenomeon setting up activity in the parietal lobe of a *pattern* of movement of elevation of the limb before him without any corresponding actual movement. Yet the episodes were followed by a "Todd" paralysis. These episodes were as frequent as 25 a day. Between attacks the biceps reflex was increased, an indication that the muscles chiefly involved in the movement of anterior extension under normal circumstances were the ones whose central sensory component of movement was felt. It was, however, now three years from onset and by this time there was a little disturbance of sense of position of the limb (destruction of the pattern at first stimulated). As the pattern became destroyed there were relatively few sensory attacks.

An angiogram was suggestive of the correct diagnosis but the signs were too slight to lead to a correct interpretation.

Three years from onset the patient had a psychoneurotic reaction to his illness, which clouded the issue and led experienced men to consider all the symptoms functional. More experienced judgment made the correct diagnosis but the surgeons were not convinced sufficiently to operate. When actual jerking of the left upper limb developed, the generalized seizures fractured the dorsal vertebra.

The electroencephalogram became correctly positive after four years. Syphilis had nothing to do with the illness, but apparently successful removal of the tumor was affected.

Case Report

Chloromycetin and Streptomycin in the Treatment of Meningitis due to B. Proteus

J. Dana Darnley, M.D.

Meningitis due to B. proteus is a relatively rare entity; McKee[1] in a review of the world literature listed only 18 reported cases up to 1944. Only about five cases have been reported[2, 3, 4] since that time.

In the years before specific antibacterial chemotherapy, B. proteus meningitis was associated with an extremely high mortality rate. Of the 14 cases reported before sulfonamides were introduced, 13 died. McKee attributes the cure of two out of the remaining four reported up to 1944 to sulfanilamide and sulfapyridine. Paine, et al.,[2] De Bakey and Pulaski,[3] Keefer, et al.,[4] report that four of the five cases recorded since 1944 responded to streptomycin. Up to this point there has been no report on the use of Chloromycetin in the treatment of B. proteus meningitis. An opportunity to observe the effect of combined chloromycetin and streptomycin treatment was offered in the case of B. proteus meningitis reported below.

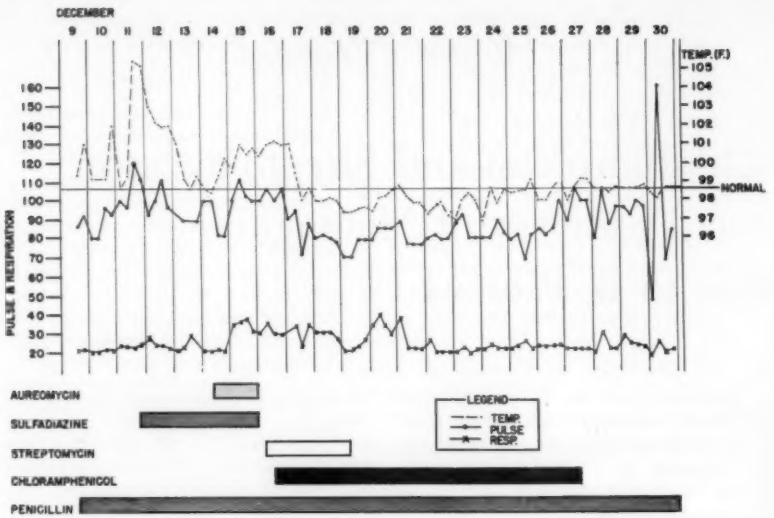
CASE REPORT

A 53 year old white male was admitted to the Bronx Veterans Hospital on December 9, 1949 to continue convalescence following his second coronary occlusion which had occurred eight weeks prior to admission. During these eight weeks the patient had been on digitalis, absolute bed rest, and mercurial diuretics as needed.

On admission the examiner noted a painful dime-sized, midline sacral decubitus, which was lined and partially filled with thick, yellow, non-odorous pus. The patient bore the appearance of chronic illness. The heart was enlarged and the heart sounds were described as of poor quality and diminished intensity. There was no evidence of congestive heart failure.

Four hours after admission the patient's oral temperature was 101° F. Low-grade fever (99° to 102°) continued for 24 hours, then rose to 105.4° F. at the end of the second day in hospital. Examination at this time showed the patient to be confused, drowsy and very restless. There was definite neck rigidity and bilateral positive Kernig's signs. The rest of the neurologic examination was normal except for the following: right corneal reflex slightly less active than left; superficial abdominal reflexes absent in all quadrants; left patellar and Achilles reflexes more active than on the right. Examination of the ears, nose and throat was negative and there was no swelling

From the departments of neurology, Baptist Hospital, St. Dominic Hospital and Charity Hospital, Jackson, Mississippi.



TIME TABLE OF CHEMOTHERAPY IN RELATION TO CLINICAL COURSE (VITAL SIGNS)

A lumbar puncture showed the following: Initial pressure of 200 mm. of water; turbid, opalescent, lemon-yellow spinal fluid with a cell count of 8100 (97 per cent polymorphonuclear cells), protein 312 mg. per 100 cc.; sugar 75 mg. per 100 cc.; routine smear and culture negative; Kolmer-Wassermann negative; and colloidal gold curve of first-zone type (5555432100).

Immeditely after the spinal puncture penicillin was administered in a dosage of 300,000 units every three hours, and the patient was given 2.0 Gm. of sodium sulfadiazine in a slow intravenous infusion. This was repeated the next day. There was a definite and favorable clinical response within 18 hours in respect to alertness and responsiveness although the patient was still slightly disoriented. His temperature fell to 99.2° F. There was no change in the neurologic picture except for the finding of Gordon and Oppenheim signs on the right. The spinal fluid, 18 hours after starting treatment, was slightly less turbid with a cell count of 760 (78 per cent polymorphonuclear cells); protein 281 mg. per 100 cc.; sugar 44 mg. per 100 cc.; chlorides, 665 mg. per 100 cc.; and negative smear and culture.

Improvement was short-lived. Twenty-four hours later the patient was again febrile and drowsy and exhibited frequent Cheyne-Stokes' breathing, but there was no change in the spinal fluid (see chart). At this point Aureomycin was started (1.0 Gm. at once and 0.25 Gm. every six hours orally), and penicillin (10,000 units) was given intrathecally. Neither of these measures altered the clinical picture. At this same time signs of congestive cardiac failure appeared, so the Digoxin dosage was doubled. Aureomycin was discontinued after 36 hours and sulfadiazine was discontinued at the same time.

December 16 a smear of the spinal fluid showed Gram-negative rods, and a report of a culture started two days previously showed B. proteus. Streptomycin was started immediately with 3.0 Gm. at once and 1.0 Gm. intramuscularly three times a day. Chloromycetin was also given (2.0 Gm. at once and 1.0 Gm. every six hours, orally).

TABLE 1

SPINAL FLUID FINDINGS

Dec.	*Initial Pressure*	*Appearance*	*Cells*	*Protein*	*Sugar*	*Chloride*	*Smear*	*Culture*
11	200	Opalescent-Lemon Yellow	8100 (97% pmn.)	312	75		Neg.	Neg.
12	140	Turbid-Lemon Yellow	760 (78% pmn.)	281	44	665	Neg.	Neg.
14 (A.M.)	190	Faintly Turbid Pale Lemon Yellow	685 (80% pmn.)	299	79	610	Neg.	B. Proteus
14 (P.M.)		Faintly Turbid Pale Lemon Yellow					Neg.	Neg.
16	260	Slightly Turbid Pale Lemon	450 (70% pmn.)	560	67	605	Occas. Gram Neg. rod	Neg.
19	130	Clear Xanthochromic	20L 1 pmn.	175	55	495	Neg.	Neg.
27	140	Clear V. sl. Xanthochromic	3L 1 pmn. 30 rbc.	108	73	630	Neg.	Neg.

six hours after the first dose of streptomycin. There was a dramatic clinical response to this combined chemotherapy within 48 hours. At that point the temperature became normal and remained so. The patient was alert and comfortable and complained only of being weak.

Spinal puncture on December 19 bore out the marked change for the better, showing an initial pressure of 130 millimeters of water, with xanthochromic but crystal-clear spinal fluid. The cell count was 20 lymphocytes and 1 polymorphonuclear; sugar 55 mg. per 100 cc.; protein 175 mg. per 100 cc.; smear and culture negative. Streptomycin was discontinued that morning after three days therapy. Chloromycetin was continued for eight more days. Throughout that period there was no fever and no signs of meningeal irritation or post-meningitic sequellae except for persistent slight disorientation as to time. The final spinal puncture on December 27 showed very faintly xanthochromic, crystal-clear spinal fluid with a cell count of 3 lymphocytes and 1 polymorphonuclear; protein 108 mg. per 100 cc.; sugar 73 mg. per 100 cc.; smear and culture negative. Chloromycetin was then discontinued and the meningitis was considered cured.

At this point, signs of cardiac failure increased. Electrocardiographic changes were consistent with a new myocardial infarct. Then, successively, there was evidence of second and third degree heart-block and, finally, of auricular fibrillation with a ventricular rate of 195 three and one-half hours before death occurred suddenly on December 30.

At autopsy, performed 18 hours after death, a section of spinal cord and meninges about six inches long was removed; this included the lumbosacral enlargement and the cauda equina. The pathologist who reviewed the case reported: "Multiple sections of the lower spinal cord (and meinges) reveal no abnormalities. There is no inflammatory disease or any evidence of a previous such process." There was also servere coronary atherosclerosis and pulmonary atherosclerosis with old and recent myocardial infarcts and recent small pulmonary infarcts, secondary to pulmonary endarteritis obliterans.

DISCUSSION

The exact nature of the offending organism in this case is felt to have been established by the finding of: 1)

two positive spinal fluid examinations (one culture and one smear), and 2) four cultures from the decubitus, all positive for B. proteus. The pathogenesis of the meningitis in this case is not entirely clear. However, we can justifiably assume that it resulted from a direct extension of the sacral decubitus ulcer. Statistically, this is an unusual source. McKee[1] lists otitis media as much the most common source of B. proteus meningitis; this patient had no evidence of otitis media. Furthermore, his blood cultures were negative and there was no X-ray evidence of osteomyelitis of the sacral vertebrae underlying the decubitus.

This patient received a total of 43.0 Gm. of Chloromycetin, 9.0 Gm. of streptomycin, 2.0 Gm. of Aureomycin, 30.0 Gm. of sulfadiazine, and 22 million units of penicillin. All but Aureomycin appear to have been given an adequate trial. It is felt that recovery from the meningitis can be attributed to the combined Chloromycetin and streptomycin therapy. Their exhibition unfortunately overlapped so that exclusive credit can hardly be given to one, but the dramatic clinical and spinal fluid improvement, which began when both were used, continued and progressed for the ensuing eight days when Chloromycetin alone was used. In connection with this, it should be noted that Long[5] believes Chloromycetin to be the agent of choice in proteus vulgaris infections. He pointed out that Chloromycetin concentration in the spinal fluid is 50 per cent that in the serum; he also pointed out that Aureomycin and penicillin are ineffectual in proteus infections.

We feel the response in this case lends support to Long's opinion, while at the same time not detracting from the already established value of streptomycin in these infections.[2, 3, 4]

CONCLUSIONS

1. Chloromycetin and streptomycin are definitely the agents of choice in B. proteus meningitis (and, undoubtedly, in other Gram-negative bacillary meningitides).

2. Due to overlapping of dosage schedules, the relative merits of Chloromycetin and streptomycin in the treatment of B. proteus meningitis in this case can not be definitely decided, but both were clearly effective.

SUMMARY

A case of B. proteus meningitis, apparently originating in an infected sacral decubitus, is reported. Successful treatment with combined Chloromycetin and streptomycin is detailed.

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Neurology

Progress and Problems in American Neurology

During the past three years the American Academy of Neurology has grown rapidly, has matured much beyond its years, and has already taken its place as a vital and dynamic force in American medicine and in world neurology. At the outset, this new society was surrounded by an atmosphere of enthusiasm on the part of younger members and by an attitude of skepticism and even doubt on the part of many of the more mature and thoughtful in the neurologic field. Time has proved the tremendous need of our society and the power and drive of enthusiastic youth. Today there is no longer any doubt regarding the need and success of the American Academy of Neurology. It has been accepted with enthusiasm by the most skeptical.

It has been necessary to undertake a tremendous amount of organizational work requiring the formation and coordination of many committees. The enthusiasm of practically every member of the Academy has been outstanding, particularly when called upon to participate in or lead activities within the Academy although faced with busy office practices and many other routine responsibilities. The phenomenal success of this organization is the result of group activity, a driving force which cannot be denied.

Our most important accomplishment has been the formation of an unrestricted neurologic society, one with which every practicing neurologist can identify himself. Its establishment has given stature to the entire field of neurology. As a strong, alert energetic champion of this specialty it has gained respect and cooperation on the part of related specialties, governmental agencies and medical educators. It is indeed impressive to have an organization of over 800 members express itself on matters related to its specialty. However, the most optimistic and strongest feature of the society is vested in its junior members—young doctors in training who will form the core of future neurology. There still remain a large number of doctors in neurologic training who are not members of the Academy and who are not making use of the benefits and indoctrination available from such an association. Every large training center in neurology in the United States is now represented within the Acad-

Presidential address to the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 12, 1951.

emy's active membership. It should be the direct responsibility of every active member to invite young doctors in neurologic training to participate in the junior membership.

As an added service to all its members, but particularly to the junior members, the Academy has initiated a series of special review courses covering all phases of basic and clinical neurology. This year the first review course in neuropathology has been offered, and the response has been most enthusiastic. The Academy now has one of the finest collections of teaching slides in neuropathology in the country, each slide documented with a complete legend. The committee on special courses is now planning to organize other courses in basic and clinical neurology to be offered at future meetings.

One of the earliest tasks of the American Academy of Neurology was to undertake a survey of the neurologically trained physicians, neurologic needs and educational facilities in this country. It was apparent that the neurologic needs far exceeded the present supply. This was realized forcibly during World War II when it became necessary to set up short training courses to obtain doctors who had some concept of the nervous system. Following the war the problem became even more pressing when the various Veterans Administration hospitals were unable to obtain neurologists to care for their many patients. In the civilian population the need was even more acute and more hopeless. As a result, many neurologic illnesses came under the care of other specialists, resulting in a lessening of interest in neurology and inadequate care to many of these individuals. In order to assay the magnitude of this problem, two committees immediately set to work, namely the educational and the survey committees. The preliminary reports and observations of these committees have already been put to use. Information has been forwarded to the United States Public Health Service to help in further planning for neurologic education and training. Two midwestern educational conferences on neurology have been sponsored by the Academy in an effort to obtain opinions of educators regarding the curriculum and the staff needs for adequate graduate and undergraduate teaching in neurology. A summary of these meetings was presented to the various medical deans at their annual meeting in October 1950. A pamphlet of the recommendations of this educational conference is now being prepared for distribution. It is indeed a milestone in American neurology that, for the first time, neurologic educators have had the opportunity to express themselves on the educational aspects of their specialty. However, the work has just begun. It is imperative that similar educational conferences be held with educators in all parts of the country so that uniform recommendations can be made.

Since the creation of the National Institute of Neurological Diseases and Blindness, the Academy's responsibility through its educational committees has increased tremendously. The National Institute of Neurological Diseases and Blindness was created in order to further research and education in the field of diseases of the nervous system and blindness. It is extremely important that the Academy participate actively in the formation and expansion of this new institute. If the neurologists do not become energetic in this matter, then, as in the past, the direction of this institute may fall into the hands of

others less well equipped, and the trend of neurologic education will suffer again.

As a result of the national mobilization program, the need for an accurate, comprehensive roster of neurologically trained physicians in the United States has become acute. It is imperative that such information be furnished as quickly as possible to Selective Service, the National Security Resources Board, the Department of Defense and other governmental and planning agencies in order that neurologists be properly assigned upon entering military service. Because of this acute need, the survey committee has accelerated its program, and a special questionnaire has been formulated and sent to all members of the Academy.

Regarding national and federal affairs, the neurologic specialty has for some time assumed a traditional attitude of over-reserved dignity and isolationism, in spite of the fact that it was destroying every opportunity for growth and strength. During World War II other disciplines represented and organized neurology in the armed services because of the disinterest on the part of the neurologists. Following that war there developed a strong trend toward federal support of medical studies. In 1946 the mental health act was passed and activated by the sum of $11,000,000, intended to support research and expand medical education in the entire field of the nervous system, both functional and organic. However, the neurologists were so poorly organized that the overall plan for the formation of this mental health institute did not include the participation of neurologists. As a result, not a single neurologist appeared on the chief medical advisory council, and neurology was completely omitted in the grants for medical education.

The American Academy of Neurology, shortly after its formation, undertook to rectify this situation and to make the importance of neurology felt in federal circles. A subcommittee on neurology in the National Institute of Mental Health and the appointment of proper neurologic representation on its advisory council were urged with successful results.

Probably the most significant development of recent times for neurology has been the establishment of the new federal institute in the United States Public Health Service, namely the National Institute of Neurological Diseases and Blindness, which offers neurology an opportunity to expand and develop adequate teaching programs in many medical schools in the country and to stimulate interest throughout the medical field.

In order to continue its part in the national and federal affairs, the Academy has formed two committees, one on legislation and one on federal affairs. Both of these committees will call on all the members periodically to participate in their activities and to voice encouragement or protest various measures concerning neurological affairs.

Finally, one of the most important activities of the American Academy of Neurology, is that of public relations, or more explicitly, that of interpreting the neurologic specialty to the public. To most people, and indeed to many physicians, the nervous system is a mysterious structure encased and hidden within bony cavities and completely dissociated from bodily activities. Unfortunately, neurologists themselves are partly responsible for this situation, since traditionally they have fostered an aloof, erudite attitude to-

ward their colleagues and patients. As a result, the nervous system itself as such is unknown, but many diseases of the nervous system have emerged as separate entities, treated by many who have had no background in the pathogenesis of the particular illness. Such diseases as poliomyelitis, multiple sclerosis, parkinsonism, central nervous system syphilis, cerebral palsy and others are unquestionably diseases of the nervous system, yet most individuals and many doctors never associate them with neurology. It is time that we as neurologists set out to inform the public of the proper nature of neurologic symptoms and illnesses, so that they will demand adequate supervision and care under properly trained personnel.

The American Academy of Neurology must organize a properly balanced program of public education by means of properly written articles, adequately prepared lectures to lay groups, and well handled publicity within the field of medicine, and finally by discussion with our colleagues and lay friends. Every opportunity must be taken to carry this educational program to all people so that by proper understanding they will demand neurologic participation wherever neurologic illness is concerned. The Academy has already made a beginning along these lines by setting up a speakers' bureau through which members will participate and discuss neurologic subjects with organizations requesting such speakers. The American Academy of Neurology has taken a tremendous step forward in educating the medical profession to the importance and significance of neurology by sponsoring the new journal, *Neurology*. Strange as it may seem, this is the first journal devoted exclusively to the subject of neurology in this country. It is our hope that by the quality of the articles in this journal and by its wide distribution it will help carry out a program of public relations and neurologic education among all those practicing medicine.

With these words I should like to thank the Academy for the privilege of the presidency during the past three years. It is my great pleasure to turn the reins of office over to the capable hands of your new president, Dr. Pearce Bailey. I should like to thank him personally for his great help during the past three years and to reciprocate by offering him my fullest support and aid in any way he deems necessary during his stay in office.

A. B. BAKER, M.D.

Not only may one part of the brain contain many centres, but a single functional centre may consist of nerve-elements that are anatomically distant—even situated in different hemispheres. Cells may act together when the nerve-fibre that connects them is many inches long, as perfectly as if they are only a hundredth of an inch apart, just as the needles of two galvanometers in the same circuit are deflected at the same moment, judged by ordinary standards, whether they are distant a foot or a mile.

—Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Neurology

BOOK REVIEWS

Medical Neuropathology

1. Mark Scheinker, M.D. 1951. Springfield, Illinois: Charles C Thomas, Publisher, 372 pages, $10.00.

This is the third volume of a series of three books on neuropathology by Dr. Scheinker, the first two having been *Neurosurgical Pathology* and *Neuropathology: Its Clinicopathologic Aspects.* The present volume deals with neuropathology in its relation to internal medicine and general pathology. The objectives of the book are "to bridge the widening gap between neuropathology and general pathology and to describe the cerebral complications of the more common internal diseases." Chapter sequences deal with the nervous system complications of cardiac diseases, functional and structural vascular syndromes, chemotherapy and exogenous toxins, and nervous alterations in blood dyscrasias and lung diseases, among others.

The organization of the book is good, and the printing and illustrations are excellent. One wonders, however, whether it fulfills the author's objectives—whether it approaches medical neuropathology in a thorough complete and up-to-date manner. In his chapters on cerebral manifestations of vascular disease, for instance, the author stresses his own well-known concepts of vasospasm, vasoparalysis, stasis and thrombosis, without disease of the vessel walls, much of which is controversial and is not adequately authenticated. Also, under reversible vascular disturbances, he lists epilepsy, arterial hypertension, and multiple sclerosis, without adequate factual support. In the discussion of the latter he mentions the work of Rucker in 1945 and Zeligs in 1947, without including the references in his bibliography. In fact, it is noted that many of his more recent references are omitted in the bibliography. There is a lengthy chapter on cerebral manifestations in cardiac disease, but the important subject of subacute bacterial endocarditis is mentioned only briefly. The important nervous system manifestations of infectious processes are hardly touched upon. In his discussion of kernicterus, listed under liver disease, it is said, "Little is known concerning the etiology and pathogenesis," and there are no references to the Rh factor.

The subject matter that this book professes to deal with is of utmost importance to the clinical neurologist and to the internist and general practitioner of medicine. It is to be regretted that the volume is not more complete and more up-to-date, and that it stresses largely controversial matters.

R.N.DeJ.

Frontal Lobotomy and Affective Behavior

John F. Fulton, M.D., 1951. New York: W. W. Norton & Company, 151 pages, $3.00.

This is a small, concisely written volume constituting the Thomas William Salmon memorial lectures of 1950. The occasion has permitted the author an opportunity to make excellent use of his gift for scientific synthesis, and at the same time to include vivid historical background material, well-chosen personal anecdotes and felicitous quotations. The comprehensive index includes both subject matter and authors' names. The detailed alphabetic references reveal concern for bibliographic accuracy.

The book presents the substrata of physiological, anatomical, pathological and psychological observations and theory which underlie the interpretation of the results of various types of frontal lobotomy procedures in man. It is especially befitting that this work be available at a time when, in the rush of the application of this operation in surgical practice, important fundamental data may be overlooked. The four sections which comprise the book deal with the historical setting, the functional anatomy of the cerebral cortex, and the more recent behavioral studies in animals; the last section deals critically with the generally more familiar lobotomy in man. In this presentation of an extensive review of the author's own studies, of those of his associates, and the appraisal of the literature, the reviewer found it gratifying that the work of one of the American investigators (James W. Papez, "A Proposed Mechanism of Emotion" Arch. Neurol. Psychiat. 38:725) was included with appropriate emphasis. Fulton records the "rich vindication" by all recent experimental work of Papez's "shrewd deduction" of the specific structural fields related to emotional experience and to emotional expression.

The book is, above all, recommended to readers who wish to acquaint themselves with the basic neurology of affective behavior. The practical-minded reader will be interested in the evidence indicating that frontal lobotomy procedures may lend themselves to more restricted operation fields and to much more specific adaption both to the nature of the mental illness and to the type of intractable pain.

A.R.V.

A Textbook of Clinical Neurology

J. M. Nielsen, B.S., M.D., F.A.C.P. Third Edition. 1951. New York: Paul B. Hoeber, Inc., 709 pages, $10.00.

In 1941 a new textbook on clinical neurology made its bow. Although certain shortcomings were noted at that time, this text was foredestined to make an enviable place for itself. This was assured by the nature of its author. A forthright person, careful, thoughtful student and observer, prodigious worker, with a love for neural anatomy and neuropathology —these qualifications are a guarantee of sound practical neurologic teaching. One sees and feels these qualities in his text.

The author's style is simple, unadorned and informal as if he were

talking to his students. He is most at home in the chapters dealing with cerebral localization, brain and spinal tumors, vascular disease and syndromes referred to the several parts of the nervous system, for in these areas his complete familiarity with anatomic structure and his studious application of careful clinical observation in terms of structural change make these chapters of decided teaching value. The chapter on cerebral localization deserves special commendation. It is richly illustrated with the very finest of photographic reproductions of the author's wealth of pathologic material. Throughout the book, illustrations are of high order.

This third edition which has been completely worked over, shows improvement in certain areas somewhat neglected in the earlier editions. New material has been added (angiography) and some topics have been rewritten to bring them up to date with current knowledge.

A reviewer is considered uncritical if he fails to frown on some part of the production or to record errors. By this time the author's friends have advised him of the latter (there are a few in this volume); with regard to weak or thin spots, it is well to point out that reviewers have biases in the same proportion as authors have strong and weak areas in their books. Authors must depend on the work of others to supplement their own knowledge gained by personal experience. Those subjects with which they have had richest experience always highlight the text just as it surely does in this case. This is an excellent text for students of neurology and is deserving of the position it now occupies in the field of medical text books.

A comment directed to the publisher seems in order. The paper is thick, adding unnecessary weight to a book of 700 pages, and the glossy paper surface acts as a reflecting medium causing annoyance when reading by artificial light.

M.G.M.

Epileptic Seizure Patterns

Wilder Penfield, M.D. and Kristian Kristiansen, M.D. 1951. Springfield, Illinois: Charles C Thomas, Publisher, 104 pages, $3.00.

This short monograph is a discussion of the clinical aura of epileptic seizures based upon an analysis of 222 patients operated upon for epilepsy. The aura of these patients is correlated with the location of the cerebral lesion, the focus of abnormal electrocorticographic activity, and, when possible, the site at which the clinical aura was produced by electrical stimulation. Although details are not given of the individual cases, there is sufficient evidence for the reader to analyze the material. Specific emphasis has been placed upon the more recently recognized symptoms of focal cerebral seizures, such as the abdominal, cephalic and automatic aura. In recent years the manifestations of focal cerebral function have been greatly elaborated by the investigations of Dr. Penfield. The mechanisms by which epileptic seizure patterns arise are still unknown, in spite of much mechanistic, and recently cybernetic, thinking. This book does not attempt the explanation, but it does clearly outline the phenomena which must be explained.

This book should be read by every

one who wishes to keep abreast with the changing concepts of cortical physiology, and especially clinicians desirous of making a differentiation between focal cortical and non-focal epilepsy.

A.E.W.

Introduction to Neuropathology

Samuel H. Hicks, M.D. and Shields Warren, M.D. New York: McGraw-Hill Book Co., Inc., 494 pages, $10.00.

This book is an unusual admixture of neuropathology, neurophysiology and neuroanatomy augmented with a little clinical neurology. Since each of these subjects is very extensive, this type of approach in such a small book has forced the authors to be very superficial in their discussions, even of the neuropathology. In some chapters this defeat is very prominent as in chapter 3, titled "Disturbances of Cerebrospinal Fluid and Intracranial Pressure Relationships," where most of the chapter is devoted to a discussion of neurophysiology rather than neuropathology. Many of the statements which are quoted as clinical facts by the authors actually are still controversial or even disproven, such as "In the absence of a positive laboratory test, the diagnosis of neurosyphilis is difficult or impossible," or "Ataxia and paresthesias are caused by loss of deep sensations and *reflexes*," or "Incoordination in poliomyelitis is due to involvement of Clarke's columns."

As a contribution to the field of neuropathology, this book has very little to recommend it. It certainly falls short of the many good books already available in the field of neuropathology.

A. B. B.

Atlas of Cross Section Anatomy of the Brain

A. T. Rasmussen, Ph.D. 1951. Philadephia: The Blakiston Company, 63 plates, $5.00.

The beautifully delineated illustrations of the internal structure of the brain, drawn by Dr. Emil Villiger from the excellent collection of Weigert sections at the University of Basel, have come to have basic importance in the study of neuroanatomy. Dr. Rasmussen has reproduced the cross sections of the brain and brain stem from the fifth section of Villiger's *Gehirn und Rückenmark*, now in its fourteenth edition and revised by Eugen Ludwig. To these he has added a series of carefully selected sagittal sections from the department of anatomy of the University of Minnesota, stained by a modified Weil iron hematoxylin method for myelin. In addition, he has to a certain extent modified the terminology, which in the most part conforms to the BNA, but adopting that of A. Earl Walker for the thalamic nuclei. The illustrations are graphically reproduced, and the full-page size of the cuts permits localization to a desirable degree. This atlas will serve as an important aid to the study and teaching of neuroanatomy.

R. N. DeJ.

Neurology

Sensory Return in Partial and Recovery Spinal Cord Lesions

Benjamin Boshes, M.D., Meyer Brown, M.D. and Richard L. Crouch, M.D.

ALTHOUGH Brown-Séquard[1] amply demonstrated by clinical observations the decussations of pathways for pain and temperature and the unilateral representation of other sensations, he had no knowledge of the location of the conductors. He believed temperature to be conducted in the central gray, pain in the posterior and lateral part of the gray matter, and tactile sensation in the anterior part of the cord. Schiff first suggested that tactile sensations were conducted by way of the posterior columns, and Gowers was perhaps the first to ascribe pain conduction to the anterolateral ascending pathways.[2]

Extensive anatomic and physiologic studies made on sensory pathways in experimental animals revealed the spinothalamic tracts to be comprised principally of crossed fibers, but to have a limited number of uncrossed fibers. Furthermore it appeared that sensation was carried largely heterolaterally, except for touch, muscle sense and to a less extent pain which were carried homolaterally. After reviewing the literature up to 1906 and adding the results of his own studies, May[2] summarized

From the department of nervous and mental diseases, Northwestern University Medical School, Chicago, and the medical neurology service, U. S. Veterans Administration Hospital, Hines, Illinois.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1951.

Published with the approval of the chief medical director, Veterans Administration. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

the state of knowledge as follows: "From the above data it seems that in the dog and lower animals no one form of afferent impulse is restricted to any one tract, not even to one-half of the cord. For each, more than one path seems open and can with time be rendered available." Turner[3] noted that monkeys with identical spinal cord lesions suffered variable amounts of sensory loss.

Petrén[4, 5] was able to study 96 cases of discreet stab wounds of the spinal cord. He found the pain and temperature loss often to be the same but touch was never so. He further observed the latter to be carried in the posterior columns and also in a lateral tract near the surface of the cord. Muscle sense, he believed, was conducted through the posterior tracts, and he added that this sensation was also carried in the spinocerebellar tracts. He thought that those fibers carrying touch either crossed early or ascended homolaterally to the medulla before crossing, and that touch and deep pressure were carried together.

Rothman[6] made similar observations on 70 cases, ten of which went to autopsy. His findings were essentially similar to those of Petrén except that he believed the crossed tract for tactile sensations to be in the anterior column and that muscle sense was carried in the anterior column. He thought that touch and pressure were conducted apart from one another. In all his cases in which hemianalgesia persisted there was, at the onset, a bilateral motor paralysis.

Fabritius[7] in 1912 maintained that pain and temperature, so-called vital sensibilities, were carried contralaterally, while touch, a so-called nonvital function, was carried homolaterally and contralaterally. He considered pain and temperature subjective, and touch and pressure, objective modalities.

Head[8] found that his grouping into epicritic, protopathic and deep sensations for peripheral nerves did not hold for spinal cord conduction, but that all degrees of heat, cold, pain and touch were each carried by a particular pathway. He also showed the possibility of a complete loss of muscle sense with preservation of touch, and preservation of muscle sense with loss of all other sensations. Heat, cold and pain were considered to be carried entirely by crossed pathways, but the degree of impairment of these three modalities was not necessarily the same. Two-point discrimination could be absent even though tactile sensation was present. The reverse could not be true, but there was a close association of two point discrimination and muscle sense. When cutaneous pain was lost deep pain was also lost, but pressure pain might be lost without loss of perception of deep pressure recognition. Stopford[9] expanded Head's con-

ception of protopathic and epicritic to include deep nerves. Here epicritic meant muscle position and joint sense, and protopathic, deep pressure. He implied a retention of these sensory qualities in the central nervous system by considering the protopathic as having thalamic and the epicritic as having cortical qualities.

Gordon Holmes[10] studied 45 cases of spinal cord injury from World War I. He found that the upper limits of anesthesia varied for different modalities and that the crossing of fibers varied in different levels of the cord. In the mid-dorsal region the crossing of pain and thermal impulses was complete in one segment. Thermal impulses crossed less rapidly than those of pain, and touch required two segments. In the upper dorsal region pain and temperature crossed in two, and above the fourth cervical segment, frequently in three segments. The decussation of pain requires five to six segments and that of thermal four to five segments. He also concluded from his studies that fibers which convey sensations from the lower spinal roots are probably placed lateral to those which have later reached the contralateral side.

Foerster and Gagel's[11] careful studies of patients with chordotomy have contributed much to the problem of association and dissociation of the modalities, and the variabilities of pathways conducting the different sensations. They found in unilateral chordotomies that there was some ipsilateral reduction of pain and more ipsilateral reduction of temperature. When there was return of some function following surgery, warm returned first, then cold and last pain. They believed that the greater return of temperature sense was due to greater ipsilateral representation of this modality and claimed a possibility for some conduction of pain even in the posterior columns. In patients with posterior chordotomy stimulation of the cephalic end of the tractus gracilis produced pain in the leg, and stimulation of the proximal end of the tractus cuneatus produced pain in arms. They stated that, in patients with posterior columns sectioned, Kroll found a reduction in the number of pain points and an increased threshold for pain. The dissociation of pain and temperature after chordotomy has been confirmed by Tilney and Elsberg,[12] Stookey[13] and others. The variable results after this procedure and the speculation on boundaries of the spinothalamic tracts by Hyndman and Van Epps,[14] Stookey,[15] Walker,[16] Kahn and Barney[17] reveal the gaps in knowledge of the extent of these pathways and of the arrangement of their fibers.

Rabiner and Browder[18] demonstrated that deep sensibility and touch are not disturbed when the ventral quadrants of the cord are cut bilaterally, or when the ventral quadrant on one side and the dorsal funicu-

lus of the opposite side are cut. Unfortunately the exact amount of cord cut in these cases could not be verified anatomically.

Brouwer[19] approached the problem of sensation from the phylogenetic point of view. He used the terms protopathic sensations for the old and vital sensations, and epicritic for the new and gnostic sensations. The latter are conducted by fibers which do not synapse in the cord, but ascend in the posterior columns to the medulla before synapsing and decussating. They have a definite pathway through the brain stem and thalamus to the post-Rolandic gyrus. The vital sensations follow pathways formed by a sensory neuron of the second order in the spinal cord and decussate in the cord. While some of them go through the spinothalamic tract, many go by short pathways, connecting at various levels in the spinal cord and brain stem. The termination in the cortex is not well known, but these fibers have a large diffuse projection here. Cortical destruction may cause a clear astereognosis without producing a defect in vital sensibility. A comparative study of the posterior columns in the scale of evolution revealed that these are not present until forms living on land are investigated. Yet in fishes the system for vital sensibility, the spinothalamic tract, is demonstrable. Brouwer associated vital with autonomic sensibility. He, therefore, divided central nervous system sensibility into two systems. The one is non-autonomic, neosensibility-gnostic. This is composed of long, simple circumscribed tracts which enter the brain in an exact localization. These impulses produce sensory observations but no feeling. The second is autonomic, paleosensibility-vital. This is composed of some long and some small tracts, complex in build which reach the cortex in a diffuse way. There is no localization and the stimuli cause sensory feeling.

It is of interest to note here that Davis, Hart and Crain[20] were of the opinion that visceral sensations are carried in the lateral funiculus of the spinal cord.

Protopathic sensation in peripheral nerve lesions purportedly recovers faster than epicritic. Some say this is so because the protopathic is a more primitive or more vital sensation. Stopford points out that the forms of sensibility which fail to recover after secondary nerve suture or which show imperfect recovery are those which have cortical representation, while those which recover early and completely are those which persist even when the sensory cortex is destroyed. He bases the difference in rate of recovery in a peripheral nerve on the readjustment and re-education which must occur in the central nervous system. Fibers subserving cortical function will require more of each.

PRESENTATION OF STUDY

The service for injuries of the spinal cord and cauda equina at the Veterans Administration Hospital, Hines, Illinois has afforded an opportunity to study the course of recovery of the various kinds of spinal cord functions in patients with partial and recovering lesions. For the study of sensory recovery only cervical and fairly high thoracic lesions were selected. In this way it was possible to eliminate complicating findings from the posterior roots and cauda equina.

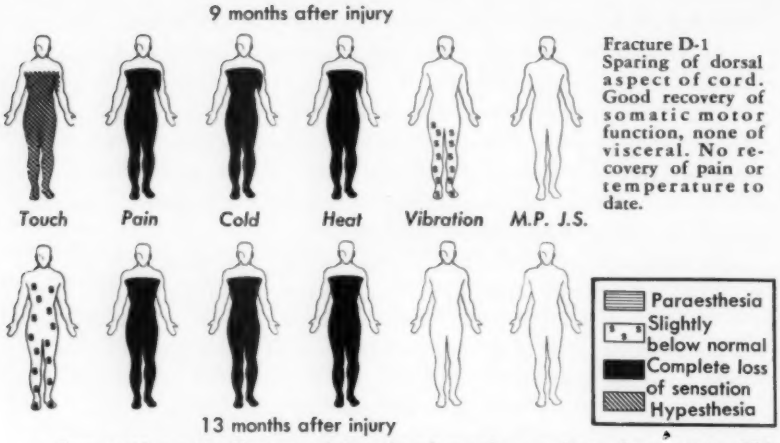
The studies were directed at the problems: (1) whether there is a pattern of sensory restitution in partial or recovering lesions of the spinal cord, (2) the amount of dissociation of various sensory modalities in both the original loss and in return of function, (3) whether there is any evidence for the philosophy of a two-system old or vital and new or gnostic type of sensory pathway, (4) whether the time of beginning return is significant in prognosing the amount of return of function.

DATA

Of 378 patients who were observed originally, 93 or 24.8 per cent had lesions which were subsequently found to be incomplete. Of these, 89 or 25.6 per cent had some kind of sensory return. In many the original disability was apparently complete as regards somatic motor and sensory and visceral motor or sensory defect. The return of voluntary motor or sphincteric control, or the restoration of some somatic sensory modalities or visceral sensation well below the level of the lesion, necessitated the reclassification of such patients as having partial or incomplete interruption of the cord.

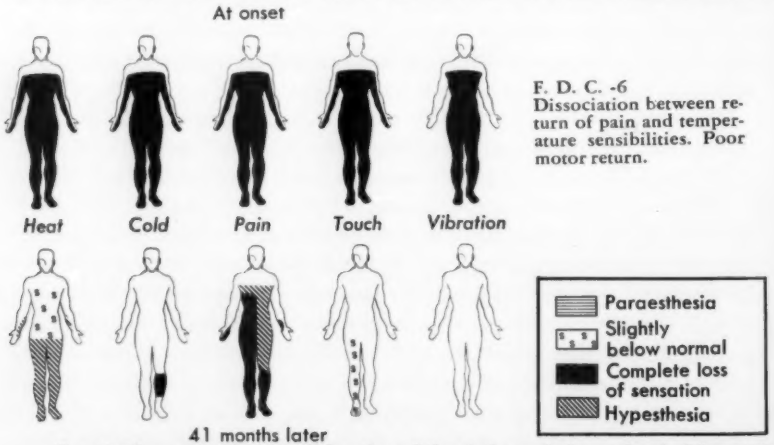
The material available for this study was disadvantageous in many respects. Most of them had service-connected injuries and were hospitalized in Army hospitals for several months before coming to the Veterans Administration. Records were not complete for many of them. The early neurologic examinations, both in the Army hospitals and during their early stay in the veterans hospital, were not done from the point of view of research. Therefore, they lacked much detail that would have been desirable. On the other hand, the large number to choose from allowed some selection of material. Some patients did offer enough detail of early study to make adequate comparisons of improvement, and the length of time of observation on some patients was a distinct asset.

The first six charts are representative of the variable patterns of recovery encountered. Obviously these are not completely illustrative as each case represents a pattern of its own.



Fracture D-1
Sparing of dorsal aspect of cord. Good recovery of somatic motor function, none of visceral. No recovery of pain or temperature to date.

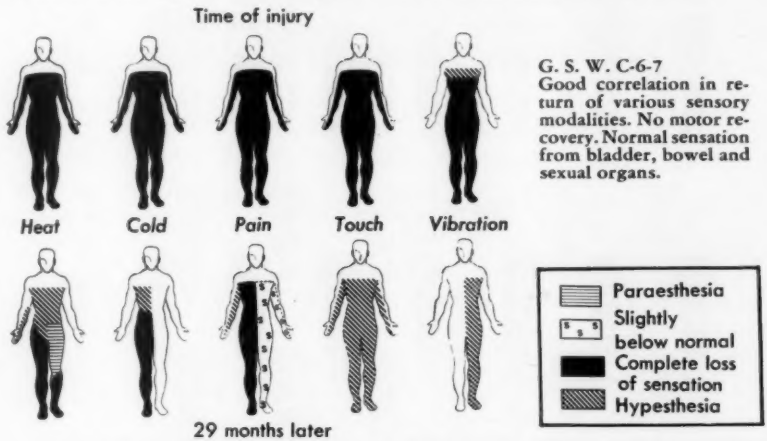
Case 1: (figure 1)—Fracture of first dorsal vertebra on September 4, 1949. This demonstrates good return of tactile sense with little or no recovery of other function. Initially there was a complete loss of sensation over the medial side of the left upper extremity and over the body from the nipple line downward. Motor control was lost completely in the left upper extremity and both lower extremities. Voluntary motor control returned to the upper extremity with almost normal strength. Some voluntary control of all muscles of the lower extremity returned, but all muscles remained very weak. There was no recovery of pain and temperature sensation, no recovery of sensory or motor functions of the bowel or bladder and no return of sexual feeling or function.



F. D. C. -6
Dissociation between return of pain and temperature sensibilities. Poor motor return.

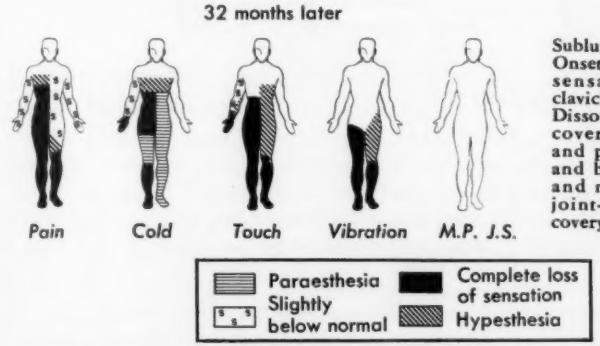
Case 2: (figure 2)—Fracture dislocation of the sixth cervical vertebra in May 1947. This demonstrates a much better return of heat and cold sensation than of pain, the reverse of what usually occurs. In comparing these modalities with tactile vibratory sensations, it seems that the greater impairment is in the lateral funiculus of the cord.

In spite of considerable recovery of sensory functions in this region, there was almost negligible return of motor function. This is the reverse of the situation in case 1.



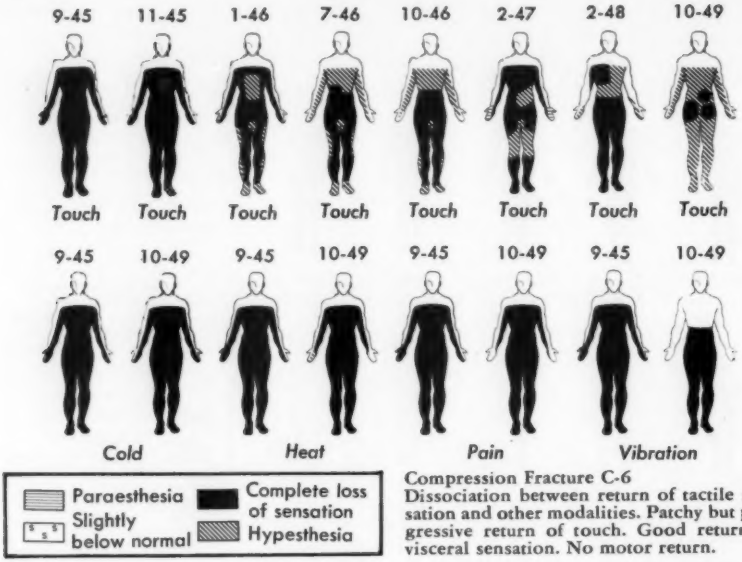
G. S. W. C-6-7
Good correlation in return of various sensory modalities. No motor recovery. Normal sensation from bladder, bowel and sexual organs.

Case 3: (figure 3)—Involvement at level of the sixth and seventh cervical segments. This patient is of interest because bladder, bowel and sexual sensation returned to almost normal state in two weeks. Here correlation between heat, cold and pain is closer than in previous cases, but temperature is slightly better perceived than pain. Motor power and sphincter control did not return.



Subluxation C-4-5
Onset: All modalities of sensation lost below clavicle. 12 months later: Dissociation between recovery of temperature and pain sensibilities, and between vibration and muscle-position-joint-sense. Motor recovery good.

Case 4: (figure 4)—Subluxation of the fourth and fifth cervical vertebrae. Pain and cold follow the same general pattern but there is a better return of cold, the pattern of the latter being somewhat irregular in arrangement. Touch follows that of pain and cold, and vibration differs only slightly from the general pattern. Muscle, position and joint sense is normal in spite of marked impairment of vibration and touch. Motor power improved to the extent that the patient could walk without crutches or cane. The greater motor return is on the same side as the greater sensory return. In this patient there was normal bladder and bowel sensation but no return of sexual functions.

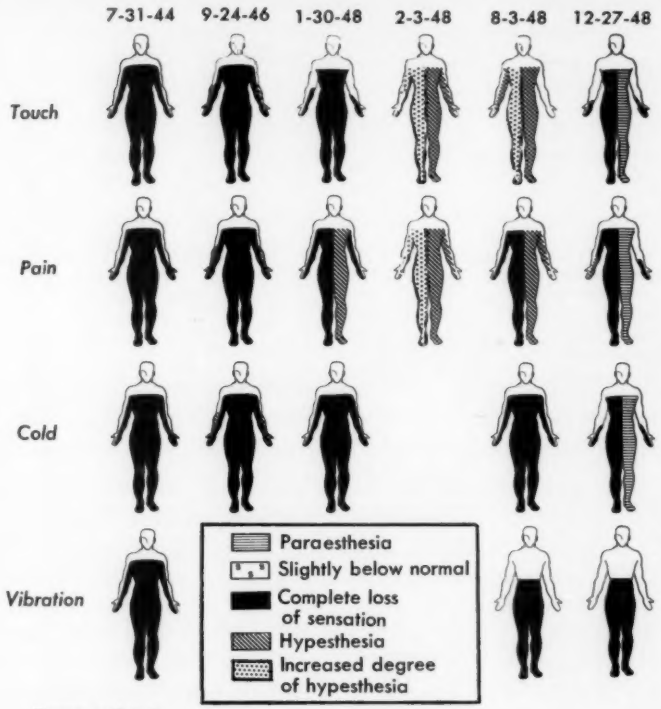


Compression Fracture C-6
Dissociation between return of tactile sensation and other modalities. Patchy but progressive return of touch. Good return of visceral sensation. No motor return.

Case 5: (figure 5)—Compression fracture of the sixth cervical vertebra in September 1945. This patient is presented because of the irregular manner of recovery of tactile sensation. There was no return of motor function or sphincter control and no return of sexual function. There was, however, excellent return of sensation of the bladder and bowels.

A study of comparative incidence of recovery of various spinal cord functions showing moderate or good return revealed that touch scored 97 per cent (table 1). The next highest percentage was vibration with 91 per cent. Cold and pain were very significantly close together 76 per cent and 78 per cent, but heat was much lower, 55 per cent. The percentage of muscle sense, 76 per cent, was much more in line with cold and pain than with vibration. Bladder and bowel sensation, 74 per cent and 70 per cent respectively, were rather closely in line with pain and cold. Sexual sensation was much lower, 52 per cent, and the percentage of return of all motor functions was lower than for return of sensory functions. Bowel, bladder and sexual functions had a lower percentage of return than did somatic motor functions.

It was thought that correlation of percentages of return between functions (table 2) might give some indication whether the return of various functions depended more on an anatomic or functional basis. The highest correlation was between heat and cold. Other high correlations were as would have been expected on the basis of anatomic propinquity, that is



Fracture C-5-6
Delayed return of sensation. Onset of sensory recovery after 3½ years. No motor or visceral return.

Case 6: (figure 6)—Compression fracture of the fifth cervical vertebra on July 31, 1944. This patient is presented because of the very long time interval between injury and beginning return of sensation. There was no indication of sensory return for three and one-half years. Here another factor might be mentioned in passing. Sensation improved up to a point and then decreased. This patient had had several episodes of severe genito-urinary infections during the earlier periods of his injury which may have delayed sensory recovery. After coming to the veterans hospital, his genito-urinary condition was controlled. Shortly after the last examination, he developed uremia and died. This case raises the question of the effect of nutritional and toxic conditions on recovery of spinal cord lesions and on the later regression of apparent recovery of sensory and motor function.

touch and muscle sense, pain and cold, heat and pain, vibration and muscle sense, touch and vibration. A lower correlation was found among sensations carried in widely separated pathways such as touch and cold, heat and touch, pain and vibration, heat and vibration. The unexpected finding for an anatomic explanation was a high degree of correlation be-

TABLE 1

COMPARATIVE INCIDENCE OF RECOVERY OF VARIOUS SENSORY AND MOTOR FUNCTIONS

	Total No. of Cases	*No. with Moderate or Good Return*	*Percentage with Moderate or Good Return*
Heat	22	12	55
Cold	33	25	76
Pain	36	28	78
Touch	35	34	97
Vibration	35	32	91
Muscle position and joint sense	21	16	76
Motor	35	21	60
Bladder-sensory	31	23	74
Bladder-motor	31	7	23
Bowel-sensory	32	22	70
Bowel-motor	32	6	19
Sex-sensory	31	16	52
Sex-motor	31	6	20

tween pain and touch, cold and muscle sense, and heat and muscle sense. Equally unexpected was the number that were noted with poor correlation between those modalities supposedly carried in the same pathways such as pain and cold, heat and pain, vibration with muscle sense.

In order to delineate this study, cases were selected where there was great variability in return of all modalities. Cases showing uniform recovery in all modalities were eliminated in table 3. Here the same general principal of correlation is found as in table 2, but a little more clearly. However, the same interesting fact was noted: there were several cases

TABLE 2

CORRELATION OF RECOVERY OF SOMATIC SENSORY MODALITIES*

Modalities	*No. of Cases*	*Per Cent with Good Correlation*	*Per Cent with Poor Correlation*
Heat with cold	23	91	9
Touch with muscle sense	21	86	14
Pain and cold	34	85	15
Heat and pain	23	78.5	21.5
Vibration with muscle sense	21	76	24
Touch with vibration	36	74	26
Pain with touch	35	71	29
Cold with muscle sense	20	70	30
Pain with muscle sense	20	70	30
Heat with muscle sense	14	57	43
Touch with cold	33	48.5	51.5
Heat with touch	24	33	67
Pain with vibration	34	30	70
Heat with vibration	23	30	70

*Correlation based on both degree and pattern of recovery.

TABLE 3

CORRELATION OF RECOVERY OF SOMATIC SENSORY MODALITIES AMONG CASES OF VARIABILITY IN RETURN OF DIFFERENT MODALITIES

Modalities	*No. of Cases*	*Per Cent with Good Correlation*	*Per Cent with Poor Correlation*
Heat with pain	8	73	27
Heat with touch	4	36.5	63.5
Heat with vibration	5	45.5	51.5
Heat with cold	10	90.9	9.1
Pain with touch	8	53.5	46.5
Pain with vibration	4	28.4	71.6
Pain with cold	13	86.6	13.4
Touch with vibration	10	73.4	28.6
Touch with cold	7	50	50
Muscle sense with heat	3	60	40
Muscle sense with cold	3	50	50
Muscle sense with pain	3	50	50
Muscle sense with touch	6	100	0
Muscle sense with vibration	6	100	0

in which there was no correlation of recovery of those modalities carried in the same pathway, such as heat, pain and cold.

The relationship of recovery of visceral sensation, bladder, bowel and sexual feeling to somatic sensory recovery is seen in Table 4. It appears that the bladder showed the highest recovery, perhaps because it had had more definitive care in the days before bowel rehabilitation programs were set up. The lack of spread of figures indicates that there was no evidence of specific localization of a visceral pathway near any one somatic sensory group. This is in spite of the fact that the percentage of incidence of recovery of visceral sensations is definitely in the same category as those of pain and cold.

TABLE 4

RELATIONSHIP OF THE RECOVERY OF VISCERAL TO SOMATIC SENSATION

	Percentage of Correlation of Return of		
	Bladder	*Bowel*	*Sexual*
Muscle, position and joint sense	80	60	56
Vibration sense	70	60	52
Touch sense	70	61	50
Pain sense	69	61	52
Heat sense	68	55	50
Cold sense	76	61	52

The correlation of the return of somatic motor function to the various sensory modalities is seen in table 5. The figures reveal a correlation in the neighborhood of only 55 to 60 per cent. Touch showed a lower level, only 38 per cent.

TABLE 5

RELATIONSHIP OF RETURN OF VARIOUS SENSORY MODALITIES TO SOMATIC MOTOR RETURN

	Percentage of Correlation of Return of						
	Heat Sense	*Cold Sense*	*Pain Sense*	*Touch Sense*	*Vibration Sense*	*Muscle Position and Joint Sense*	*Visceral*
	to	*to*	*to*	*to*	*to*	*to*	*to*
Somatic motor return	61	57.5	56	38	48.5	55	59.5

Table 6 reveals that most of the cases destined to recover, 73.9 per cent, start to do so in the first three months, but occasionally recovery is delayed and may even start at four years.

TABLE 6

RELATIONSHIP OF CASE DISTRIBUTION TO TIME OF ONSET

	Time of Onset of Recovery					
Months	*0-3*	*4-6*	*7-9*	*13-15*	*22-24*	*46-48*
No Cases	17	2	1	1	1	1
Per cent	73.9	8.7	4.3	4.3	4.3	4.3

While good to excellent recoveries are seen chiefly in cases where improvement started early, this is not an absolute rule (table 7). A patient whose return of sensations started after two years had excellent recovery, while one with no recovery for four years made a fair improvement after this time.

TABLE 7

DEGREE OF RECOVERY OF SENSATION VS. TIME OF ONSET

	Time of Onset of Recovery in Months					
Degree Recovery	*0-3 17 cases*	*4-6 2 cases*	*7-9 1 case*	*13-15 1 case*	*22-24 1 case*	*46-48 1 case*
Poor	0	1				
Fair	3		1			1
Good	7			1		
Excellent	7	1			1	

The latter case was known to have bladder and kidney infections at frequent times up until a few months before sensation began to return. This raises the question of the influence of toxic and nutritional states upon recovery of sensory functions. There were nine cases in our study in which improvement went to a definite point and then regressed. Some of these regressions could be correlated with infections. One patient began to develop some movements in the lower extremities. With the onset of a bladder infection this was lost and never regained.

DISCUSSION

These studies were pointed at the questions: (1) whether there is a

pattern of sensory restitution in partial or recovering lesions, and (2) whether there is any evidence in the spinal cord for setting up a philosophy of a two-system, protopathic and epicritic, in the sense that Brouwer has described these sensations in the central nervous system.

A review of the sensory pattern of the sample cases indicates at once that there is no constant mode of sensory return as the modality recovers. In some, the level simply drops in a segmental manner. In another, the recovery may appear in isolated parts well below the lesion, as the saddle area, and proceed upward. In still another, one modality may recover on one side which may not correspond at all anatomically to the recovery of other modalities.

Thus recession of sensory loss follows no definite pattern in these cases, possibly because the initial involvement was patchy as is often demonstrated anatomically, or because in one area the longitudinal fibers may be partially or totally fractured, while in another they may be interrupted only for a time by edema or small hemorrhages.

The question of resistance of the various fasciculi to trauma or their recoverability may be related to question 2, indicating fundamental differences between tracts which carry one or another modality.

A study of the recovery of the various modalities demonstrates that touch, which is represented in the posterior columns as well as in the spinothalamic tract, recovers best while heat, one of the so-called vital sensations, recovers the least often. Vibration, a new modality phylogenetically, recovers almost as often as touch. Bladder and bowel sensations recover about as often as pain and cold, suggesting, as in the theory of "autonomic-vital" association, a possible propinquity of pathways in the lateral funiculus.

Correlations of rate and degree of recovery of pairs of sensory modalities should help determine whether the involvement is due to simultaneous injury of the tracts as they run together, or whether there is an actual difference in vulnerability and reparability of the tracts, whether they run in one bundle or not.

Heat and cold which course through the spinothalamic tract recover together most often. Both are "vital" functions. In contrast heat and vibration or pain and vibration are very low in correlated return. The modalities run in different tracts and one, heat, is "vital," the other, vibration, not vital, but "gnostic." However, the "vital-gnostic" theory or the paleo vs. neosensibility theory does not hold up in this material. Cases where the recovery is patchy show essentially perfect correlations for vibration with muscle sense or touch with muscle sense. This indicates that the newer posterior columns can recover rapidly and that the re-

covery is anatomic. When the column recovers, all modalities contained therein return.

As regards visceral sensation, that from the bladder returns first, perhaps because more care is usually given to this paralyzed part. The percentage correlation gives no clue as to whether the pathway for the conduction of visceral sensation lies near one or another definitely localizable somatic sensory tract. As indicated before, the figures for sexual sensation may be low because the patient usually associates such feeling with ejaculation and the return of visceral motor function is quite low.

The question of whether the return of somatic motor function is correlated with any sensory modalities still remains unanswered. Such a return is definitely not associated with touch or vibration, modalities which accompany the motor fibers in the peripheral nerve. The 55 to 60 per cent correlation of motor return with other modalities is only a little above a chance finding.

Unfortunately, our data do not have sufficient detail of the immediate post-traumatic period to enable us to determine at what time exactly a given sensory modality began to recover. However, taking all sensation together, it would appear that most cases destined to recover begin to do so within the first three months. Occasionally recovery is delayed by infection, nutritional and metabolic factors, and the onset may not occur until late. Such delay does not of necessity mean poor recovery. Although the best returns are seen in patients who begin to recover within three months after injury, late onsets, even at two years, may go on to an excellent restitution of sensory function.

SUMMARY

1. Of 378 patients with traumatic lesions of the spinal cord, 93 or 24.8 per cent had lesions which were subsequently found to be incomplete.

2. The pattern of return was quite variable. Most frequently there was a recession of the anesthesia and paralysis in a segmental manner. At other times function returned first in the sacral regions and ascended. In others there was a gradual return of function over the whole affected area at the same time. Somewhat of a variation of this method was a patchy return over the affected area.

3. There was a high percentage of correlation of sensory modalities carried in the same fasciculi indicating that the return of sensory functions was on an anatomic rather than on a functional basis.

4. The problem of "paleosensibility" or "vital" and "neosensibility" or "gnostic" was considered, but did not appear applicable in the material studied.

5. The time after injury for return of function was usually within three months. There were some exceptions to this. Although good recovery is generally associated with early recovery, this is not invariably true.

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Neuromyelitis Optica with Xanthochromia and Spinal Block

Howard D. McIntyre, M.D. and Aurelia P. McIntyre, M.D.

In 1942 a case of neuromyelitis optica was reported with yellow fluid and complete spinal block.[1] Chiasmal exploration revealed cystic arachnoiditis of the optic nerves and chiasm. Following the later development of transverse myelitis, laminectomy disclosed cystic adhesive arachnoiditis of the spinal cord from the fifth to the seventh laminae inclusive. This case will be briefly reviewed and a similar case will be discussed.

Case 1:—A woman aged 38 years was seen in April 1931 with the chief complaint of blindness, the onset of which had been gradual, beginning in late January 1931. Neurologic findings included bilateral papilledema of 2½ diopters, secondary optic atrophy, dilated fixed pupils and bilateral pyramidal tract signs. Sensory examination was normal at that time.

Chiasmal exploration revealed cystic arachnoiditis of the chiasm and optic nerves with displacement of the optic nerves from their normal position by constricting adhesions. There was also an increased amount of fluid in the cisterna chiasmatis. This patient was completely blind, and vision did not improve after the surgical procedure. The patient was again seen in November 1933 with spastic paraplegia involving both lower extremities. Neurologic findings at this time consisted of pyramidal tract signs, paralysis of the bladder and complete loss of sensation extending as high as the fifth dorsal dermatome. The spinal fluid was yellow and coagulated in the test tube on withdrawal. Complete spinal block was present. Laminectomy from D3 to D7 inclusive exposed cystic arachnoiditis in the entire operative field, the cysts being filled with yellow fluid. Microscopic examination of the fluid content of the cysts revealed lymphocytes, polymorphonuclear cells and macrophages. Evacuation of the contents of the cysts did not improve the paraplegia.

Case 2:—A man aged 27 years was admitted to the hospital on January 25, 1943 with symptoms of paraplegia, urinary incontinence and failing vision in the right eye. The onset of these symptoms had been rather sudden, beginning on January 7, 1943.

Neurologic findings consisted of amblyopia and papilledema in the right eye, the swelling measuring 2½ diopters, spastic paraplegia with the appropriate pyramidal tract

From the department of neurology, University of Cincinnati, Cincinnati, Ohio.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 12, 1951.

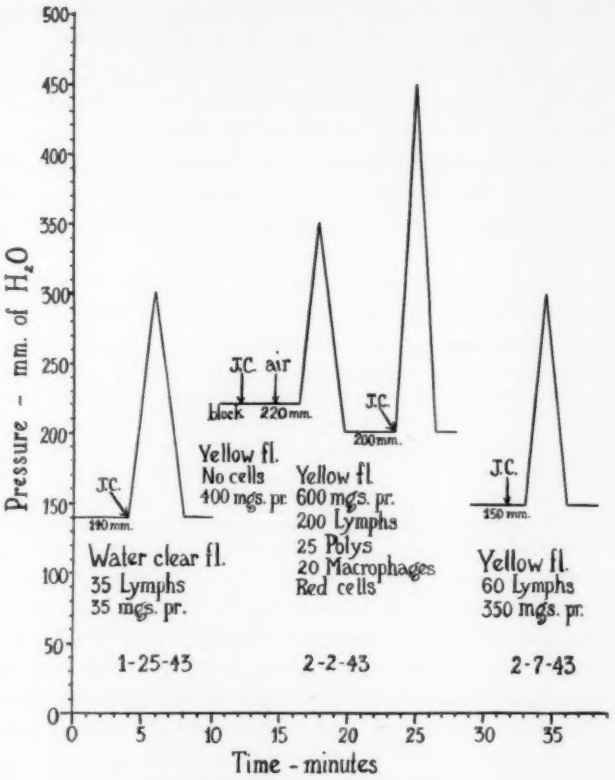

FIG. 1. Spinal manometrics—case 2.

signs, and urinary incontinence. In addition there was a sensory level of anesthesia extending as high as the seventh cervical dermatome on the right and to the first dorsal dermatome on the left. Spinal puncture released clear fluid without block. The fluid contained 35 lymphocytes per cu. mm. and 35 mg. of protein per 100 cc.

On January 28, 1943, 21 days after the onset of optic neuritis in the right eye, optic neuritis with 2 diopters of swelling and a central scotoma were noted in the left eye. On January 29, 1943 the sensory level had ascended to the fourth cervical dermatome and there was almost complete paralysis of both arms. On January 30, 1943 the sensory level had ascended to the second cervical dermatome and the patient required the aid of a respirator for breathing.

On February 2, 1943, spinal puncture released yellow fluid under pressure of 200 mm. of water (figure 1). This fluid contained no cells. Complete spinal block was present. After the injection of 20 cc. of air into the subarachnoid space there was a copious flow of spinal fluid which contained lymphocytes, polynorphonuclear cells, macrophages and red blood cells. Following the air injection the dynamics were normal. The spinal

dynamics were normal on February 7, 1943 and March 1, 1943. On March 22, 1943 spinal block was again present and was again released by air injection.

Repeated spinal punctures over the next few months, the last one in August 1943, revealed normal dynamics with clear fluid; however, the paraplegia and bladder incontinence remained unchanged. The sensory level had descended to the fifth dorsal dermatome at the time of the last examination in June 1950.

Air injection has been used to release spinal block in three cases. One patient recovered completely, and in the other two cases the block was relieved but the paraplegia and sensory level remained practically unchanged.

Concerning the prognosis in neuromyelitis optica, the disease may pursue several different courses, and may abort with the subsidence of the optic neuritis[2] as is seen in the following case.

Case 3:—A girl aged 14 years was seen February 15, 1944, complaining of rapid failure of vision of a week's prior duration. Neurologic findings were bilateral amblyopia with dilated fixed pupils, Bilateral papilledema measuring 2½ diopters, and bilateral pyramidal tract signs. Sensory examination was normal. Lumbar puncture released clear fluid under normal pressure with normal dynamics. The fluid contained 56 lymphocytes and 5 polymorphonuclear cells per cu. mm. The protein was 150 mg. per 100 cc. Within three weeks after the onset of amblyopia, vision began to return. The pupils reacted to light and within the following six months the patient gained serviceable vision without scotoma. A definite bilateral pallor of the optic nerves still remains in 1950.

Neuromyelitis optica may also abort with the subsidence of the symptoms of isolated transverse myelitis. This eventuality is rare. More frequently the transverse myelitis remains unchanged although the optic neuritis may not appear later, or the transverse myelitis may rapidly ascend and death may ensue due to respiratory paralysis, as evidenced by the following case.

Case 4:—A youth aged 14 years was first seen on June 25, 1932, with spastic paraplegia, bilateral pyramidal tract signs, urinary incontinence and complete sensory loss extending to the fifth dorsal dermatome. Lumbar puncture released yellow fluid which coagulated on withdrawal. Complete spinal block was present. On August 6, 1932 a laminectomy was performed from D3 to D7 inclusive. On opening the dura, extensive cystic arachnoiditis was seen identical with the picture observed in case 1. Examination of the contents of the cysts removed by aspiration disclosed lymphocytes, polymorphonuclear cells and macrophages. The patient's symptoms were not relieved by the operation and on September 26, 1932, he died of ascending myelitis with respiratory paralysis.

Rarely, a case of neuromyelitis optica may recover both from the blindness and the myelitis as evidenced by the following case.

Case 5:—A white man was seen in 1933 with bilateral amblyopia, papilledema, and pyramidal tract signs. Within ten months he regained serviceable reading vision. In 1935 he experienced an attack of transverse dorsal myelitis with spastic paraplegia, urinary incontinence, and sensory loss below the level of the lesion. Within the following six months he regained a serviceable gait. Mild residual pryamidal tract signs persisted.

In summary of the prognosis of neuromyelitis optica it can be said that the prognosis for the return of serviceable vision is good. The authors have seen only one survival case which remained permanently blind. Remission of both visual and cord signs may occur, and in this clinical respect the disease resembles multiple sclerosis. The prognosis of the myelitis is more unfavorable than is that of the optic neuritis because of two factors: (1) the danger of ascending myelitis; (2) permanent paraplegia due to compression of the swollen cord by the rigid dura and spine. The overall mortality is at least 50 per cent in the initial attack. Years may elapse between the attack of optic neuritis and the later development of transverse myelitis, as is shown by the following case.

Case 6:—A white man aged 45 years was seen in July 1949 with the neurologic findings of complete dorsal transverse myelitis. Previous history disclosed that he had suffered an attack of bilateral optic neuritis five years before, from which he had recovered, regaining serviceable vision. Ophthalmoscopic examination in July 1949 revealed bilateral optic atrophy of mild degree with a relative bilateral central scotoma. One month after the onset of dorsal myelitis the patient developed symptoms of a rapidly ascending myelitis and died of respiratory paralysis.

A discussion of neuromyelitis optica always brings up several questions. Is neuromyelitis optica a form of multiple sclerosis? Is acute multiple sclerosis identical (as far as pathogenesis is concerned) with remitting multiple sclerosis? Is the difference in the clinical course of acute multiple sclerosis and remitting multiple sclerosis due merely to the variation of toxicity of the same noxious agent as well as variation in the powers of resistance of the host? The work of Kabat, Wolf and Bezer[3] has distinct bearing on this last question. In this work on the experimental production of demyelinizing disease, it was shown that animals of the same species vary greatly in their reaction to the same dose of the noxious agent (white matter and adjuvants).

Scheinker[4] believes that the acute and chronic forms of multiple sclerosis compose one nosologic unit. He compares the chronic form of remitting multiple sclerosis to chronic phthisis, while he compares the acute form of multiple sclerosis to "galloping consumption." The English hold a similar view,[5] namely, that spontaneous acute disseminated encephalomyelitis, acute multiple sclerosis and acute myelinoclasis designate the same neurologic entity and that the pathology in these acute conditions is identical with that seen in the more chronic forms of multiple sclerosis, with certain minor exceptions. Scheinker[6] also believes that neuromyelitis optica is almost if not identical with acute multiple sclerosis. Hassin,[7] on the other hand, believes that neuromyelitis optica should be classified as a distinct morbid entity and should be separated from

acute and chronic multiple sclerosis. He points to the constancy of involvement of the optic nerves and spinal cord together with the involvement of gray matter as well as of white matter in neuromyelitis optica.

In favor of Hassin's thesis that neuromyelitis optica is a distinct clinical and pathologic entity are the ten survival cases of neuromyelitis optica that have been followed over a period ranging from seven to ten years. In no case has evidence of focal recurrence of demyelinizing disease in the hemispheres, brain stem, or spinal cord, above the permanent transverse lesion, been observed. A long term observation of many surviving cases of neuromyelitis optica is clearly indicated with this point in mind.

It has been said by some who believe that neuromyelitis is a distinct clinical and pathologic entity that, whereas optic neuritis is common in neuromyelitis optica, it occurs only rarely in multiple sclerosis. This statement is somewhat misleading. Bilateral optic neuritis with and without papilledema is common in acute multiple sclerosis and is not unknown in chronic remitting multiple sclerosis as was observed in seven cases, one of which is briefly reported here.

Case 7:—A man aged 30 years was seen in 1932 in his initial attack of multiple sclerosis with the symptoms of diplopia, paraparesis, bilateral pyramidal signs, and Brown-Sequard syndrome, with loss of temperature and pain perception extending as high as the sixth dorsal dermatome on the right side. He recovered completely from these symptoms, and ten years later developed retrobulbar optic neuritis with central scotoma in both eyes. The attacks of optic neuritis were separated by about two weeks.

As to clinical remissions there is evidence that such remissions occur in neuromyelitis optica as well as in acute and chronic multiple sclerosis. Remissions occur frequently in acute multiple sclerosis, although they are usually of short duration and several remissions and exacerbations may follow one another with great rapidity even within a nine months period,[8] as will be demonstrated by a representative case report. Remissions also occur in neuromyelitis optica. In nearly every instance of this disease there is a remission of the visual symptoms and in some cases remissions of both visual and myelitic symptoms.

Although remissions do occur in acute multiple sclerosis it has been observed that most cases eventually terminate fatally, death ensuing in from two to nine months after the onset of the first symptoms. The striking feature of acute multiple sclerosis is that in this disease one sometimes sees, as in the remitting form of the disease, exacerbations and remissions following one another with great rapidity. If one were to compress the long drawn out course of remitting multiple sclerosis measured in years, into a few weeks or months, the similarity of the remissions and exacerba-

tions of the acute type of the disease to those of chronic multiple sclerosis is striking, as is evidenced in the following case.

Case 8:—A woman aged 35 years had enjoyed excellent health until December 15, 1933, at which time she was stricken with paraplegia involving both lower extremities. This condition improved rapidly and by February 1, 1934 she had completely recovered. On February 15, 1934, she developed the symptoms of loss of sensation in the left face, arm and trunk down to the eighth dorsal dermatome. These findings completely remitted within a two weeks' period. On March 13, 1933 the symptoms of diplopia, anesthesia of the left side of the face, corneal areflexia, nystagmus, ataxia of the legs, bilateral pyramidal tract signs, and intention tremor of the left hand appeared. These findings cleared up completely within a three weeks' interval and the patient was completely well and doing all of her housework. On January 2, 1934, the symptoms of labial herpes, ataxia of the left arm, bilateral paraplegia with anesthesia extending to the tenth dorsal dermatome, bilateral pyramidal tract signs, incontinence of bowel and bladder, dysarthria, dysphagia, and euphoria, developed. She grew steadily worse, the transverse myelitis ascended and she died of respiratory paralysis on September 9, 1934. One sees in this patient a remitting and exacerbating demyelinizing disease progressing to a fatal termination in less than nine months after the first symptoms of the illness.

That the similarity of acute multiple sclerosis to neuromyelitis optica is superficial is seen in the following case.

Case 9:—A woman aged 45 years was admitted to the neurologic service on November 29, 1949, with amblyopia and bilateral optic neuritis of two weeks' duration. Over the next two months the condition grew rapidly worse, she developed hyperreflexia, scanning speech, nystagmus, paresis of both lower extremities, more marked on the left side; the paresis eventually progressed to quadriplegia. She became dysphagic and dysarthric. No sensory findings were demonstrated at any time during the course of her illness. She lapsed into coma and died on February 5, 1950.

Representative sections from the nervous system revealed extensive areas of demyelinization in the optic nerves and chiasm, in the centrum semiovalae and basal ganglia, the pons, medulla, and spinal cord. Relatively few of these plaques were related to blood vessels.

Such cases of acute multiple sclerosis superficially resemble neuromyelitis optica in two respects: (1) the presence of bilateral optic neuritis with and without papilledema, (2) the occurrence of myelitic symptoms which, however, are not transverse. Acute multiple sclerosis differs from neuromyelitis optica in the important respect that in acute multiple sclerosis many focal demyelinizing lesions are seen in the brain, brain stem and spinal cord.

SUMMARY

1. Two cases of neuromyelitis optica complicated by adhesive spinal arachnoiditis with yellow cerebrospinal fluid and spinal block are presented. In case 1 adhesions of the spinal arachnoid and chiasm were noted at operation. In case 2 it was demonstrated by spinal manometrics that

the demyelinization process preceded the adhesive arachnoiditis. Air injection demonstrated that the cysts contained polymorphonuclear cells, lymphocytes, macrophages and red cells. In case 2 an interval of about 18 months elapsed between the development of optic neuritis and the later development of transverse myelitis. In case 2, 21 days elapsed between the involvement of the right and left eyes.

2. An attempt is made to bring cases of isolated optic neuritis and isolated transverse myelitis into relation with neuromyelitis optica.

3. It is demonstrated that remissions and exacerbations may occur in the acute forms of multiple sclerosis just as they do in the remitting types of this disease.

4. Acute and remitting multiple sclerosis compose one nosologic unit insofar as pathogenesis is concerned. The clinicopathologic differences are to be explained on the basis of toxicity of the noxious agent and the powers of resistance of the host.

5. The question of the identity of neuromyelitis optica with acute and remitting multiple sclerosis is still unsettled, with the preponderance of evidence in favor of Hassin's view that neuromyelitis optica is a distinct morbid entity. The resemblance of acute multiple sclerosis to neuromyelitis optica is superficial. Those who believe that acute and remitting multiple sclerosis are identical with neuromyelitis optica must explain the constancy and selectivity of involvement of the optic nerves in conjunction with the transverse lesion of the spinal cord. They must also explain the important fact that surviving cases of neuromyelitis optica do not later show focal demyelinization in the brain, the brain stem or the spinal cord above the permanent transverse cord lesion.

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Perioral Reflexes

K. A. Ekbom, M.D., B. Jernelius, M.B.
and E. Kugelberg, M.D.

IT HAS been known since the close of the nineteenth century that in some individuals it is possible to produce a contraction of the lip musculature by means of a tap on the upper lip. The first observations were made on children in connection with investigation of the Chvostek phenomenon (Escherich:[1] "phénomène de la bouche"; Thiemich:[2] "Lippenphänomen"). Toulouse and Vurpas[3] were the first to study more systematically the lip contraction, "le réflexe buccale," in normal and pathologic conditions. These two authors are at times cited, although incorrectly, as the discoverers of the reflex. The reflex has since been studied by a number of authors.[4-18]

The appearance of the reflex has been described with slight variations. The description most frequently given is as follows: The mouth closes and the lips shoot forward as in whistling. The reflex is obtained by a tap on the upper lip, either on one side or in the midline. Escherich[1] observed that the reflex might be asymmetrical; a tap on the one side drew the upper lip over to the opposite side. Toulouse and Vurpas[3] observed that the lip contraction could also sometimes be produced by a tap which did not fall directly on the lips but in their vicinity. Lip contraction following a tap on the nose was later described as a separate reflex (the naso-labial) by Margolin[9] and Astvatsaturoff.[19] A contraction of the lips may also be produced by stimuli other than a tap. Thus Oppenheim,[20] by pressing the lips and tongue with a glass rod, was able to produce a series of rhythmic sucking and chewing movements in children with cerebral diplegia and in a comatose woman with status epilepticus. Oppenheim's reflex is hardly identical, however, with the earlier mentioned lip reflex. A similar reflex is observed in cases of insulin coma.

The naso-mentalis reflex described by Simchowicz[21] resembles the lip

From the department of clinical neurophysiology and Neurological Clinic, Serafimerlasarettet, Stockholm, Sweden.

reflex, but is not identical with it. It consists of an elevation of the chin when the tip of the nose is tapped. This reflex is reported to be particularly lively in postencephalitic parkinsonism.

Regarding the frequency of the lip reflex in normal and pathologic conditions, extremely varying results have been published. Some state that the reflex is absent in normal subjects,[3, 5, 6, 12, 16] while others[11, 14] found it in about 10 per cent of cases. A few found it very often in normal persons, Divry and Evrard[15] in 44 per cent, and Schlezinger[18] in a "large percentage." It is commonly believed that the lip reflex occurs frequently and is lively in cases of extensive, especially bilateral, cerebral lesions such as general paresis, cerebral arteriosclerosis, pseudobulbar palsy, hydrocephalus and parkinsonism. In mental cases without severe anatomic cerebral lesions, the lip reflex has been encountered in very variable frequencies, ranging from 10 per cent[16] to 83 per cent.[11]

The nature of the lip phenomenon has also been the subject of different views. Some authors[1, 5] considered it was a question of direct mechanical stimulation of the muscle, but the majority consider it to be a reflex. Others have suggested that it might be part of the sucking reflex.

In short, it may be said that lip reflex has not been ascribed any true diagnostic importance. This is quite natural when one considers that investigators have reached completely different results regarding the frequency of the reflex both in normal and pathologic conditions.

Recent studies have furthermore shown a double component in the electromyographic records of the periocular and perioral facial reflexes evoked by tapping.[22] Since the facial reflexes thus have a more complicated composition than is revealed by purely clinical investigation, it has been necessary to complement the earlier observations by more exact methods. In the present investigation the perioral reflexes have been clinically observed and electromyographically recorded both in normal persons and in persons with pathologic conditions.

METHODS

Muscle action potentials were led off mainly by plate electrodes connected to one or sometimes two differential amplifiers operating a double beam cathode ray oscilloscope. When one amplifier was used the other beam of the oscillograph was connected to an oscillator for time recording in intervals of 2 or 10 msec. In some experiments concentric needle electrodes were used instead of plate electrodes in order to obtain a more accurate localization of the activity to definite muscles.

The reflex studied was elicited by tapping the face with a metal rod or stroking the skin with a blunt needle. At the moment of contact with the skin the stimulus started the sweep of the oscilloscope which had been suppressed, and the course was recorded on film.

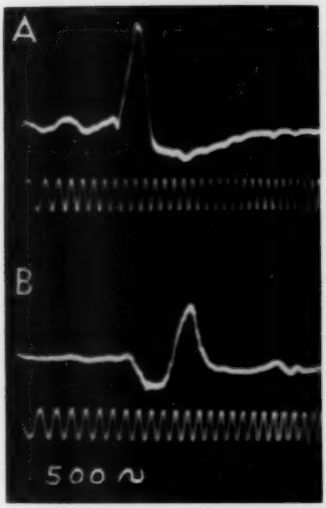

FIG. 1. *(left)* Early reflex discharge recorded by plate electrodes. Tapping of the upper lip evokes a well-synchronized discharge coming after a latency of about 13 msec. *A*. From orbicularis oris muscle. *B*. From mentalis muscle.

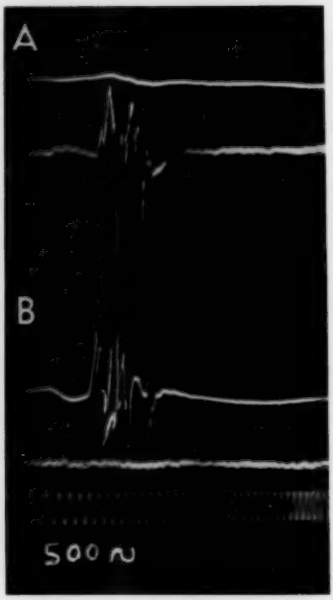

FIG. 2. *(right)* Early reflex discharge recorded by needle electrodes inserted in the left (upper tracings) and right (lower tracings) upper lip. *A*. Tapping of the right side evokes a reflex discharge on the right side only. *B*. Tapping on the left side evokes a reflex discharge on the left side only.

RESULTS—NORMAL CONDITIONS

At an early stage it became obvious that it was impossible to classify the perioral reflexes on the basis of clinical observations alone. What appeared to be homogeneous reflex responses were revealed on electromyographic analysis to consist of several components. Neither could the reflexes be divided up merely according to their adequate stimulus. It is often not clear which structure is stimulated with the more common methods of eliciting the reflex, such as tapping and stroking. The skin and muscles form an anatomic continuity which is easily movable over the bone and, therefore, facilitates transmission of mechanical stimuli to neighbouring structures, thus rendering it often impossible to determine even the point of elicitation.

The responses to mechanical stimuli have been arbitrarily classified according to reflex time as early and late reflexes. A third type of response designated the oculomentalis reflex, which seemed to be associated with the blink reflex, has been added.

1. *Early Reflexes:* A sudden tap on the upper lip elicits a contraction of the orbicularis oris muscle. The contraction is accompanied by a well-synchronized action potential coming 11 to 16 msec. after the tap (figure 1a—recorded with plate electrodes). Other perioral muscles, such as the mentalis, respond in the same manner to tapping on the perioral region (figure 1b). If concentric needle electrodes, which facilitate a more exact localization of the activity, are inserted in the upper lip a few centimeters from the midline on either side, a tap delivered to one corner of the mouth will produce activity only from the orbicularis oris on the same side (figures 2a and b). Thus the reflexes appear to be strictly unilateral in spite of the fact that the function of the orbicularis oris muscle is mainly bilateral.

If the threshold for the release of the reflex is low or if the tap is hard, the reflex is often bilateral. If in similar cases the lip is fixed at the midline by being pressed against the teeth with a finger, the activity on the contralateral side is considerably diminished. Thus the spread of the reflex to the contralateral side depends, at least to some extent, on the spread of mechanical stimuli. The possibility of a fraction of the reflex being bilateral on strong stimulation cannot be excluded altogether. That which remains may, however, be explained by transmission of a certain amount of concussion, unavoidable in loose, easily displaced tissues such as that of the lips.

The fast reflex in the orbicularis, examined in 20 cases, appears to be constant in normal individuals. In half the cases a distinct contraction was observed even clinically on concussion of the lip. In the remaining cases the reflex was not sufficiently strong for its presence to be determined with certainty, since it was obscured by the movements evoked mechanically by the tap itself. In this group, however, its presence was revealed by the electromyogram in all cases.

The appearance of the reflex response was subject to great individual variations. As stated earlier, in half the cases it was clinically impossible to be certain whether a reflex really was present on concussion of the lip. In a number of cases contraction was clearly unilateral on concussion of one side of the lip and strongest in the upper lip. In a few cases the response was lively with bilateral contraction of the whole orbicularis oris muscle. Finally, in isolated cases contractions occurred also of other muscles, such as the mentalis, so that the chin and lower lip were elevated. Twitching of the ala nasi was also observed.

2. *Late Reflexes. Orbicularis Oris Muscle:* A tap on either the upper or the lower lip produces in addition to the early synchronized response ('e' in figures 3a and b), also a late response ('l'). This

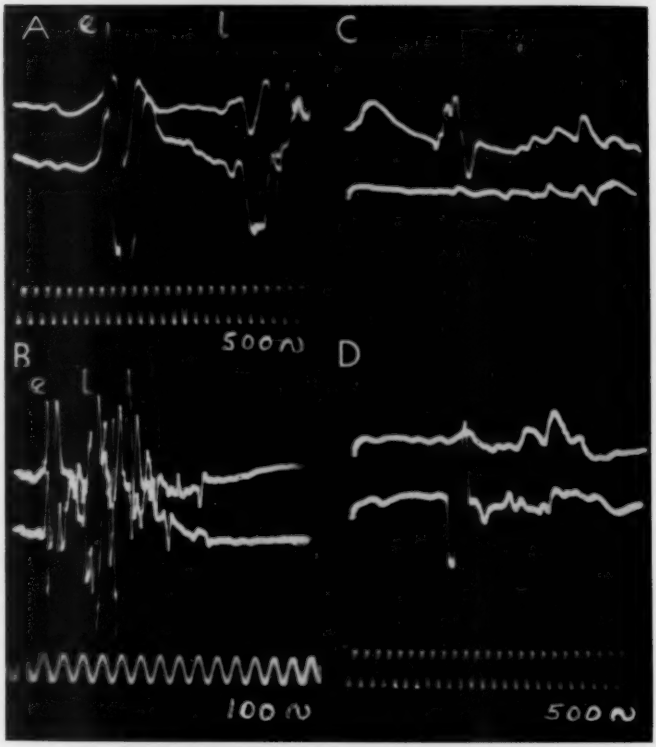

FIG. 3. *A.* and *B.* (same subject) show a double reflex response in the orbicularis oris muscle. The early reflex (e) is followed by a late asynchronous response (l); *A.* fast, and *B.* slow, sweep speed. *C.* and *D.* (another subject) show a unilateral first response and a bilateral second response recorded by needle electrodes inserted in the left (upper tracings) and right (lower tracings) upper lip. Responses were elicited by tapping the left (*C.*) and right (*D.*) sides of the lip.

appears after a latency of 25 to 40 msec. and, in contrast to the early response, is bilateral (figures 3c and d). The late reflex was observed in 14 out of 20 normal subjects on applying a moderately strong tap. The discharge is asynchronous and lasts considerably longer than the early reflex discharge (figure 3b). The muscular contraction, therefore, lasts longer than in the early reflex. Clinically it is difficult to distinguish between them, particularly if the reflex is released by a tap, since a lively first reflex is bilateral, and the speed and duration of the contraction are difficult to determine.

The late reflex varies considerably in strength from day to day and

minute to minute. It is not always symmetrical and may be considerably more lively on the one side than on the other. If the reflex is lively it can be elicited by stroking the lip.

Mentalis Muscle: A late reflex of the same type as that observed in the orbicularis oris muscle also occurs in the mentalis muscle, elevating the chin. Sometimes the lower lip is also elevated, in which movement the contraction of the mentalis muscle plays the greater part.

The late reflex in the mentalis muscle often appears simultaneously with the late orbicularis oris reflex, and if both are lively a general coordinated contraction in the perioral region is obtained. However, although both reflexes generally appear simultaneously, there are cases in which the one is lively while the other is weak.

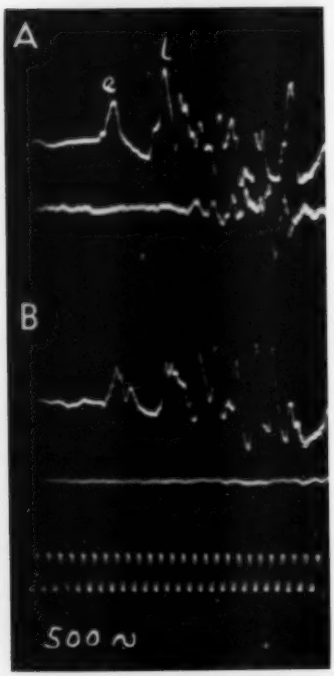

FIG. 4. Oculomentalis reflex. Tapping the bridge of the nose evokes a double reflex discharge in the eyelids (upper tracing in *A*. and *B*.) and a late response in the mentalis muscle (lower tracing in *A*.), but none in the upper lip (lower tracing in *B*.).

3. *Oculomentalis Reflexes:* A contraction of the chin musculature (acoustico-oculomentalis and optico-oculomentalis reflexes) often occurs when the subject is startled by an unexpected loud noise, or when an object is suddenly brought into the field of vision. A reflex response of the same type is also easily evoked by a tap on the bridge of the nose even if the subject has his eyes closed. This latter is shown in figure 4a, where the activity was led off from the upper eyelid (upper tracing) and the mentalis muscle (lower tracing). The activity from the eyelid shows the typical double response. A well-synchronized reflex response after 13 msec. (e) is followed by a long asynchronous response after 23 msec. (l).[22] The activity in the mentalis muscle was of the same type as the second response in the orbicularis oculi muscle, but came after a longer latency, 32 msec. The activity was chiefly localized in the chin and no activity was registered from the upper lip (figure 4b).

The optimal area for production of the reflex by mechanical stimu-

lation lies around the eye, which is also the optimal area for production of the blink reflex. If an area in the vicinity of the mouth is stimulated no reflex is obtained. Therefore, it is obvious that this reflex in the mentalis muscle is not identical with the earlier described mentalis reflex. Out of 21 normal cases it was observed clinically in six and electromyographically in 18. The reflex appears to be associated with the latter of the two blink reflexes in that all stimuli which evoke the mentalis reflex also evoke the late blink reflex.

PATHOLOGICAL CONDITIONS

Parkinsonism: Nine patients with parkinsonism were examined both clinically and electromyographically, and an additional 64 patients only clinically. In 24 of the latter the disease was probably of postencephalitic origin. The perioral reflexes in these patients, however, did not differ from those in the others of this group.

In 21 of the patients who were examined only clinically, no lip reflexes could be observed with certainty. Observable reflexes were present in 43 of the patients clinically; lively reflexes were fairly common. In 19 of the patients a clinically observable mentalis reflex was also present.

In the nine patients examined electromyographically, all reflexes earlier observed in normal cases were present. In three of the patients both the early and late reflexes in the orbicularis oculi muscles were very lively, as also the mentalis reflexes. In these patients there was no definite relationship between the condition of the perioral reflexes and the condition of the muscle stretch reflexes of the limb.

Amyotrophic Lateral Sclerosis: Five patients, of whom one had symptoms of bulbar palsy, exhibited lively perioral reflexes which, on electromyographic analysis, consisted of both early and late reflexes. Elevation of the lower lip and chin on concussion of the upper lip also occurred in all these cases.

DISCUSSION

Contraction of the lip and chin muscles resulting from tapping the upper or lower lip are clearly reflex in nature, as shown by the latent period. However, if the tapping is applied more laterally on an area between the corner of the mouth and the zygomatic bone, the contraction of the lip which follows is generally due either to solely mechanical stimulation of motor fibres in the facial nerve branches (Chvostek's sign) or to the stimulation combined with an early reflex reaction.[23] The interference of direct mechanical stimulation of motor nerve fibres renders clinical interpretation of the nature of the response still more difficult without electromyographic analysis.

The perioral reflexes which are obtained by tapping have certain characteristics in common with the blink reflexes similarly elicited. Both in the orbicularis oris and the orbicularis oculi muscles there is an early, mainly unilateral reflex contraction accompanied by a well-synchronized electrical discharge, and a late bilateral reflex contraction accompanied by an asychronized discharge. The early type of reflex is definitely identical in the two muscles and has characteristics which make it probable that it is a question of a myotatic reflex.[22] The functional significance of the late orbicularis oris reflex as well as that of the late mentalis reflex is not clear, and in adults is certainly very slight, at least compared with that of the late orbicularis oculi reflex. Thus the threshold is much higher for the perioral reflex than for the orbicularis oculi reflexes. The double component in the perioral reflexes is very clearly marked in the electromyogram, but much more difficult to interpret by purely clinical observation, although experienced neurologists have observed it.[24]

All the perioral reflexes described here are normal reflexes and more or less constant in normal individuals, although often difficult to demonstrate clinically. The great variation in the strength and appearance of the reflexes in normal persons renders it difficult to draw a dividing line between normal and pathologic conditions. Lively perioral reflexes, however, were seen much more often in the pathologic material investigated here, consisting of cases of parkinsonism and amyotrophic lateral sclerosis, than in the normal material.

Regarding the afferent pathway of the early and late periocular reflexes elicited by tapping, it has been shown that the afferent arc is in the trigeminal nerve,[22] and there is no reason to believe that the condition is not the same for similar reflexes in the perioral muscles.

The long latency for the mentalis reflex which accompanies the blink reflex suggests a more complicated central pathway than that for the late orbicularis oculi reflex elicited by mechanical stimulation. The oculomentalis reflex might be related to the startling character of the stimulus rather than to the mechanical stimulation of the skin proper and so be subserved by higher pathways.

SUMMARY

Reflex contractions of the orbicularis oris and mentalis muscles evoked by tapping the face have been studied clinically and electromyographically. The following reflexes were observed in normal persons:

1. An early reflex response electromyographically characterized by a well-synchronized discharge coming after a latent period of 11 to 16 msec. This response is mainly unilateral, and was present in the orbicularis

oris in all 20 subjects examined. Clinically, the reflex was observed in 10 of the cases.

2. A late reflex response electromyographically consisting of an asynchronous discharge coming after a latent period of 25 to 40 msec. This response is bilateral although it may be stronger on one side. It was observed in the orbicularis oris in 14 out of 20 normal subjects. The reflex is usually equally brisk in the orbicularis oris and mentalis muscles, but may sometimes be strong in the one muscle while absent in the other.

3. A late reflex contraction of the mentalis muscle associated with a strong blink reflex. The reflex is most easily elicited by mechanical stimulation of the periocular region, and was electromyographically observed in 18 out of 21 subjects.

The reflexes here mentioned vary considerably in strength in normal individuals, but very lively reflexes were much more common in cases of parkinsonism and amyotrophic lateral sclerosis.

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Behaviour Deficits Following Diencephalic Lesions

John S. Meyer, M.D. and John Hunter, M.B.

HUNTER and Jasper[1] have produced states of arrested movement simulating petit mal seizures in the unanaesthetised cat by implanting electrodes in the intralaminar region of the thalamus and stimulating this area. In one animal it was noted that a permanent and marked change in the responsive state of the animal resulted following a series of stimuli, consisting of a poverty of spontaneous movements and an apparent increase in response threshold to all forms of sensory stimulation.

This interesting result, together with clinical observations noted following diencephalic damage in man, was responsible for the present study. The aim of the present series of experiments has been to make well localized lesions in anatomical components of the diencephalon in order to observe behavioral and electroencephalographic changes following such lesions, in the hope of clarifying some of the neural mechanisms related to sleep and unresponsive states.

In man it is well known that diencephalic damage may modify greatly the state of responsiveness. In 1941, Cairns, Oldfield, Pennybacker and Whitteridge reported a case of "akinetic mutism" and unconsciousness associated with a cyst of the third ventricle.[2] The patient lapsed into a state not of sleep but of inertia and silence, with the eyes open and following movements.

In 1947 Penfield and Jasper, in a discussion of regions of the brain which are indispensable to consciousness, described an exploration of the third ventricle under local anaesthesia during which "pressure upon the medial nuclei of the thalamus produced a period of advancing stupor, followed by coma from which, fortunately, the patient shortly aroused."[3]

From the department of neurology and neurosurgery, McGill University, and the Montreal Neurological Institute.

This work was presented in part by Dr. Wilder Penfield at the Canadian Neurological Association meeting in Halifax, June 1950, under the title of "Highest Level Seizures."

We have studied three other cases in man in which localized damage in the diencephalon produced a prolonged state of unresponsiveness, with no movements other than postural, with loss of speech, but with the eyes open and following moving objects.

Papez, in a discussion of post mortem studies of lesions associated with changes in consciousness, stated that the mammillo-thalamic tract or some part of it leading to the anterior thalamic nucleus was demyelinated or disconnected in some cases.[4]

The results of experimental damage of the diencephalon in animals have not always been consistent. It may well be that some of the conflicting results reported by different investigators can be explained by differences in criteria of evaluating sleep in experimental animals and also by poor localization of many of the lesions.

Spiegel anl Inaba made stab wounds in subcortical structures in rabbits and dogs and concluded that a somnolent state could be produced by thalamic damage.[5] The hypothalamus did not appear to be damaged. Exact localization of their lesions was necessarily limited by the nature of the methods used.

Ranson and co-workers[6-8] in a comprehensive study of lesions in the hypothalamus concluded that somnolence and catalepsy may be produced in the cat by damage "to some structure or structures in the neighbourhood of the mammillary bodies, such as the posterior hypothalamic nucleus, the supramammillary area, the lateral hypothalamic area and the region just caudal to the mammillary bodies." A more specific localization could not be given. In the monkey, Ranson concluded that "all the evidence from this series of experiments points to the lateral hypothalamic area as the region bilateral destruction of which leads to somnolence."

Hess, in his exhaustive studies of electrical stimulation in the diencephalon of the cat, found that following stimulation of the lateral part of the massa intermedia in the region of the mammillo-thalamic tract, the cat settled down to sleep.[9] Following bilateral coagulation of large midline areas relatively caudal in the hypothalamus of the cat, he reported complete passivity and loss of spontaneous activity with partial restitution after eight days. Hess also reported a state which he termed "adynamia" with stimulation in the region of the lateral and anterior hypothalamus.

Harrison was not able to produce somnolence in cats by a stimulating current.[10] He reported somnolence and subnormal motor initiative without abnormal plasticity in cats with either hypothalamic or thalamic lesions. The hypothalamic lesions were located in the lateral hypothalamic

area. The thalamic lesions extended bilaterally from the pulvinar to the anterior thalamic nuclei.

Miller and Spiegel produced sleep and catatonia lasting several days by lesions in the ventral thalamus of the cat. The hypothalamus was intact.[11]

Ward has noted changes of responsiveness and piloerection following extirpation of the cingulate gyrus of the Macacus rhesus.[12] This finding is of special interest in view of the known anatomical connections of the cingulate gyrus with the anterior thalamic nuclei. Lashley and Sperry severed the cortical connections of the anterior thalamic nuclei in rats and demonstrated that there was no loss of olfactory discrimination. The animals required forced feeding for several days following the lesion.[13] Patton, Ruch and Walker noted that besides loss of taste following bilateral lesions in the vicinity of the nucleus ventralis posteromedialis of the thalamus in monkeys there were also signs of immobility, catalepsy and somnolence.[14]

Electroencephalographic changes following diencephalic damage in man are said to be characterized by rhythmic slow waves of frequencies of the order of 1 to 4 per second.[15, 16] Kennard and Nims[17] and Kennard[18] found that in monkeys "lesions of the thalamus alter the pattern of cortical EEGs in general but most markedly in the postcentral areas." These changes were usually the production of waves at 6 to 8 cycles per second. Obrador[19] reported that a lesion limited to the hypothalamus and basal region of the brain abolished the spontaneous electrical activity of the cerebral cortex; and after lesion of the thalamus or its thalamocortical pathways, the cortical activity also disappears. Recent studies by Lindsley, Bowden and Magoun[20] and the present authors do not support these findings, however.

METHODS

Experiments were made on 23 cats and two monkeys (Macacus rhesus). (Only preliminary experiments have been made on the monkey).

Following pre-operative observation and recording of temperature, pulse and respiration, each animal was anesthetised intraperitoneally with Nembutal (0.5 grain per Kg.). The head was shaved and six sterile dural screw electrodes were placed permanently into the skull in uniform frontal, temporal and occipital positions which were determined by means of a standard scalp marker. The permanent electrodes facilitated taking postoperative electroencephalograms without anesthesia. They consisted of 4/40 gauge brass nuts soldered to the heads of short brass screws which were fixed into the skull through drill holes (figure 1A). Small bolts attached to shielded lead-off wires could then be attached and detached readily.

The animal was then placed in the Horsley-Clarke stereotaxic instrument and preoperative electroencephalograms were recorded. Skull electrodes were connected by their

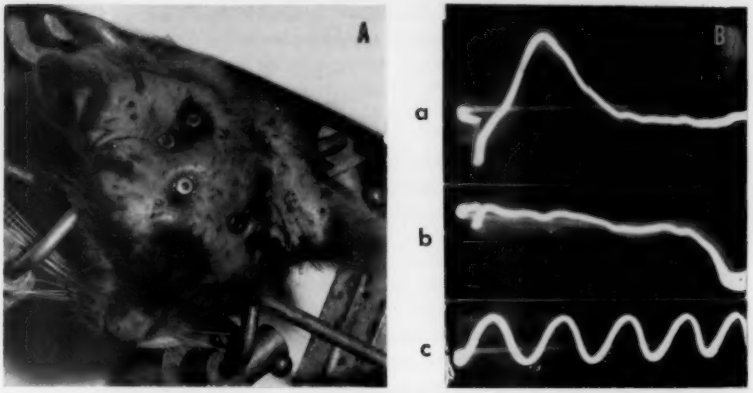
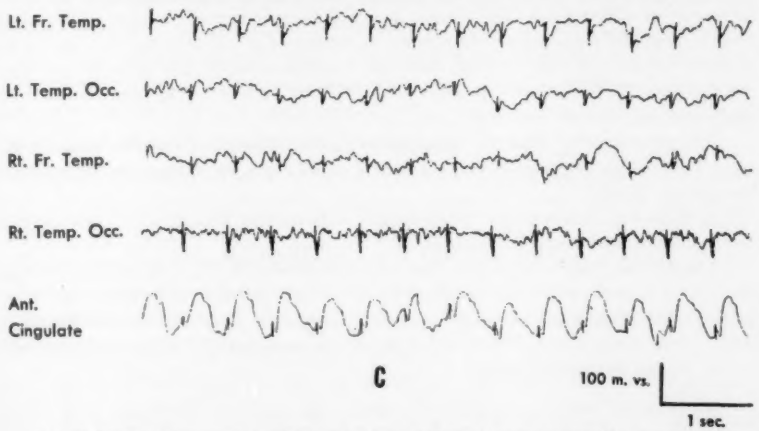


FIG. 1. *A*. Method used for EEG recordings. The screw units remain in the skull and detachable shielded lead off wires are readily attached by means of a threaded screw.
B. (a) (Cat P8-398) Response obtained from ipsilateral anterior cingulate electrode when mammillo-thalamic tract was stimulated just above mammillary body. (b) Abolition of response after lesion was made. (c) Time base 100 cycles per second.



C. (Cat P8-343) Responses obtained only from ipsilateral anterior cingulate gyrus during placement of coagulating electrodes in the anterior thalamic nuclei on the left side.

shielded wires to six channels of a five-stage R. C. coupled amplifier and then to a power amplifier driving a six pen Offner 'crystograph'; in later experiments a 'dynograph' ink-writing unit was employed.

Two types of bipolar electrodes were used for diencephalic coagulations, the tips being separated by 1.5 to 2 mm. The first type consisted of steel needles held in a heat resistant ceramic cylinder, sealed with cement and insulated to the tips with two coats of silicone insulating varnish and oven-dried. The second type consisted of platinum wires sealed into pyrex capillary glass tubes and were found to be more satisfactory.

A midline trephination was performed under aseptic conditions and the needles were lowered into the area to be studied using coordinates modified from the atlas of Ingram, Hannet and Ranson.[21] In many experiments, the final position of the electrodes was controlled by the electroencephalographic response to thalamic stimulation, e.g., stimulation of the dorsomedial nucleus produces a primary response in the gyrus proreus of the cat.*

For localization in the mammillary bodies and anterior thalamic nuclei, recordings were made from electrodes on the anterior portion of the cingulate gyrus while the former structures were being stimulated (figure 1C). Abolition of the response to stimulation after the lesion was made gave positive evidence of satisfactory coagulation, as in figure 1B. This method of control gave accurate placement within half a millimeter. The stimulus was a condenser discharge of 1 or 2 milliseconds duration. The strength of the stimulus was regulated between 0 and 14 volts peak by means of a potentiometer. The frequency of the stimulus varied from less than 1 to 40 per second. The shock artefact was eliminated by leading the stimulus output to ground through a balancing potentiometer connected across the stimulus output.

Electrocardiographic tracings were recorded across the forelimbs in several experiments before and after the ablations, by connecting a lead electrode surrounded by a saline pad to the input of one channel of the ink-writer.

Electrolytic coagulations were made in the diencephalon by passing direct current through the bipolar electrodes from a constant current power supply, having a maximum output of 25 milliamperes. The current flow was independent of resistance changes of from 0 to 25,000 ohms across the output. A current of 3 milliamperes was passed for measured periods of time, varying from one to three minutes. The polarity was then reversed and the procedure repeated. Both bilateral and unilateral coagulations were made.

The postoperative behavior, temperature, pulse, respiration and electroencephalogram were studied for periods varying from 2 to 62 days, the average period of study being about 10 days.

Animals with marked behavioral changes were studied with 16 mm. color cinematographic records for exact comparison.**

The animals were sacrificed by Nembutal anesthesia and the brain perfused through the carotid arteries with saline followed by an isotonic solution of formalin and gum-acacia.[22] The brain was fixed in 10 per cent formalin and serial coronal sections (20 u thick) were made. Every fourth and fifth section was stained for myelin[23] and with aniline-thionin for Nissl substance.

RESULTS

The results of these experiments on 23 cats and two monkeys fall into three groups, as follows:

1. A group of three control animals which showed no abnormal behaviour following implantation of the electrodes in the diencephalon without making coagulation.

*This method was employed by Hunter and Jasper in a previous series of experiments.

**A 16 mm. color film entitled "Studies of the Effects of Diencephalic Lesions on the Behavior of Unanaesthetised Cats" has been prepared to summarize the results of this work.

2. A group of 15 experimental animals which demonstrated marked behavioral deficits consisting of poverty in spontaneous movements following coagulation in or adjacent to the mammillo-thalamic tract extending from the mammillary bodies to the anterior nuclear group of the thalamus, these changes often being associated with electroencephalographic abnormality.

3. A group of experimental animals which showed either slight or no behavioral change following coagulation in other areas of the diencephalon than those made in the second group and which showed no marked electroencephalographic abnormality.

1. *Control group.*

This group consisted of three cats which underwent identically the same procedure as the other experimental animals except that no electrolytic lesions were made. These animals comprised part of a stimulation series which was in progress at the same time.[1]

Bipolar electrodes were placed vertically in the thalamus, cemented to the skull and left in place for periods varying from one to two or more weeks. Postoperative behavior revealed no significant change; two of the animals attained almost their pre-operative state of activity (including feeding themselves) several hours after operation. Electroencephalograms of these animals taken immediately postoperatively or after several days showed very little if any change from that observed in the unoperated animal under similar conditions of recording.

Anatomical placement of the electrodes was in the left anterior nuclear group in two animals, and in the nucleus centralis medialis and the right nucleus centrum medianum in the remaining animal.

2. *Group showing marked behavioral deficits consisting of apathy, akinesis, catalepsy, unresponsiveness and similar states.*

Anatomic analysis of this group shows that they are best considered after division into the following subgroups:

(a) Lesions involving the anterior nuclei of the thalamus in the neighborhood of the rostral end of the mammillo-thalamic tract (nine cats).

(b) Lesions in the region of the middle of the mammillo-thalamic tract and nuclei of the internal medullary lamina (two cats, one monkey).

(c) Unilateral and bilateral lesions of the mammillary bodies and hypothalamic portion of the mammillo-thalamic tracts (three cats).

Summaries of the protocols and representative protocols of this group of animals will be given.

2a. *Damage to the anterior nuclei and the termination of the mammillo-thalamic tract.*

The animals in this group showed similar postoperative behavior with

one exception which will be discussed later. In general, this group of animals showed profound behavior deficits following operation. For the first 10 days they showed no spontaneous movement but remained in a crouched position with only occasional changes in posture. Some days after operation, if given painful stimulation, they moved sluggishly a few paces and then returned to their immobile state. The eyes remained open and followed moving objects, the corneal and pupillary reflexes being intact. The hopping, placing, righting and deep tendon reflexes were present and unchanged without exception. Painful stimulation also caused movements of the tail and ears or withdrawal of a previously extended limb. One animal, on painful stimulation, moved forward until its head struck a wall where it remained until it slowly settled to a crouch position as if by gravity. Some animals showed a tendency to maintain abnormal postures when placed in them but there was never the same degree of catatonia as was seen in lesions in the region of the lower end of the mammillo-thalamic tract.

If the animals remained alive they showed no inclination to eat and required forced feeding by gastric lavage for the first 10 to 13 days. By the 14th day the animals began to feed spontaneously. They also showed a striking docility and any form of rage reaction was either difficult or impossible to elicit.

After prolonged observation up to 65 days the animals showed a gradual return to normal behavior, but the return was never complete. Until the end of observation the animals remained docile, easily handled, and showed no resistance to being held upside down or by one limb.

These animals also showed a marked lack of grooming, and it was necessary to brush and wash them repeatedly.

Frequently the animals were noted to have piloerection more marked along the trunk and back, together with tachycardia and hyperthermia. The heart rate usually was greater than 200 beats per minute, and hyperthermia was considered to be the cause of death in two animals which died on the third day after operation. The temperatures recorded were as high as 104°-105° F.

One animal (P8-379) in which the lesion did not involve the mammillo-thalamic tract was considered to be abnormally quiet following operation but not to the same degree as the other animals in this group. Following stimulation she would walk readily and purred on stroking. Piloerection was present, the temperature was 103.4° and the heart rate was 240 per minute at the time of sacrifice on the third postoperative day. This was the only animal in which an erosion of the gastric mucosa was found.

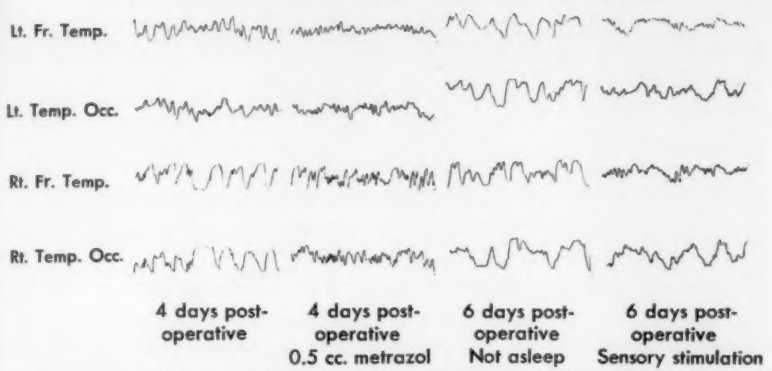


FIG. 2. (Cat P8-237) EEG without anethesia following lesions of the anterior nuclei of the thalamus. Note effect of sensory stimulation. (Compare with figure 5B).

Anatomical analysis of the lesions revealed that there was damage in the upper end of the mammillo-thalamic tract in all these animals with the one exception described. In all animals there was complete or partial damage to the anterior nuclear group of the thalamus. In some animals there was also partial damage to neighboring structures such as the stria medullaris, the paraventricular nuclei, the nucleus centralis anterior, the nucleus medialis dorsalis (pars medius), the habenular nuclei, nucleus rhomboideus, and the anterior portion of the nucleus lateralis, but similar damage to such structures was not found consistently in the majority of the animals in this group.

A typical protocol representative of this group is cat P8-237:

Lesion: Bilateral destruction of the anteromedial, anterodorsal and midline nuclei anteriorly, with bilateral damage to the anterior part of the dorsomedial nucleus and interruption of the superior portion of the mammillo-thalamic tracts.

Observations: Twenty-four hours postoperatively the animal lay immobile with its eyes open and capable of following moving objects. When placed on its feet, it slowly assumed a crouch posture which it maintained. For five days no spontaneous movements were observed other than postural changes; painful stimulation would provoke a few steps with a low crouched gait. On the sixth postoperative day, complete passivity was noted; abnormal postures could be produced without resistance from the animal; hopping, placing and righting reaction were intact. After 10 days the animal began to drink spontaneously, and when placed on the floor moved with a crouched gait to a corner where it remained.

Passivity was still marked after four weeks. There was no resistance to being held upside down or in other abnormal postures. Reactions to painful stimuli were subnormal and no rage reactions could be produced (figure 2).

After 65 days, the maintenance of fixed position for several minutes was still apparent. Throughout the postoperative course, pilo-erection, lack of grooming and a rapid heart rate of over 200 beats per minute were found repeatedly.

Electroencephalography of Group 2a. Records were taken under anesthesia during operation and immediately after the lesion was made. In most instances records were also made without anesthesia on several postoperative days.

In general, the immediate postoperative records (excluding Cat P8-379) showed a change from normal to a generalized predominantly slow background of low voltage, on which was superimposed occasional relatively high voltage slow waves with frequencies varying from 1 to 4 per second. These were usually of random type, but were frequently observed to occur in short rhythmic bursts. The records made three to four days postoperatively showed an even greater degree of slow background activity than the earlier records. Still present was the superimposed 2 to 4 per second random or rhythmic slow waves.

In Cat P8-379, the immediate postoperative record and later records showed very little if any change from the pre-operative recording. This was the only animal in the group which did not have damage to the mammillo-thalamic tract.

2b. *Damage to the midportion of the mammillo-thalamic tracts and nuclei of the internal medullary lamina.*

In the one monkey (P8-412) in this group, no anatomical studies have been made. The lesion is estimated to be in the midportion of the mammillo-thalamic tract. Following operation the animal became docile and stolid.

Cat P8-383:

Lesion: Partial damage to the nuclei of the midline (including reuniens, arcuatus, centralis medialis, rhomboideus and anteromedialis) and severance of the midportion of the mammillo-thalamic tract.

Observations: During the two days of postoperative survival the animal's movements were slow and lethargic. Moving objects were followed by the eyes but no response to auditory or tactile stimulation could be elicited. Body temperature was 102° F. and heart rate 260 beats per minute. On two occasions the animal walked several paces; on the first occasion it walked off the examining table and would have fallen, and on the second attempt it walked into a wall, stopped and remained motionless.

Cat P8-396:

Lesion: Extensive destruction of the midline nuclei from the pulvinar to the anterior nuclei. The medial fibres of the mammillo-thalamic tracts were destroyed and some damage to the nucleus medialis dorsalis (figure 3C).

Observations: Postoperative temperature was 105° F. and heart rate greater than 200 beats per minute. Without stimulation akinesis was marked. Catatonic postures were spontaneously assumed and could readily be produced (figures 4a, 4b, 4c and 4d). Muscle tone was normal. These abnormalities persisted until death occurred on the fifth postoperative day.

Electroencephalography of Group 2b. Apart from a tendency toward

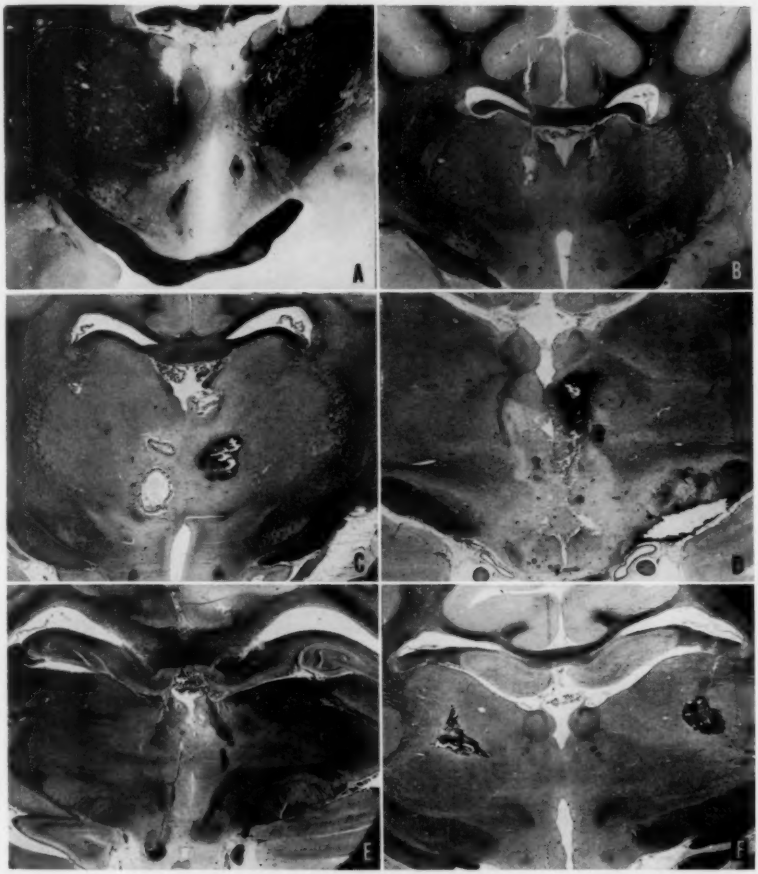


FIG. 3. Photos taken looking caudad so that lesions on the right appear on the left in the picture. All sections Weil stain (x7). *A.* (Cat P8-235) Bilateral lesions in the region of the anterior nuclear group of the thalamus. *B.* (Cat P8-352) Damage to the region of the anteriomedial nuclei of the thalamus. *C.* (Cat P8-396) Lesion in the anterior portion of the thalamus in the region of the intralaminar nuclei. *D.* (Cat P8-395) Bilateral destruction of the mammillary bodies and mammillo-thalamic tracts. There is an area of hemorrhage in the region of the left habenulopeduncular tract. *E.* (Cat P8-398) Unilateral damage confined to the right mammillary body and mammillo-thalamic tract. Cataleptic attitudes were maintained by this animal. *F.* (Cat P8-370) Bilateral lesion involving the lateral nuclei of the thalamus.

a slower frequency background, the postoperative records showed little abnormality when compared with those taken pre-operatively.

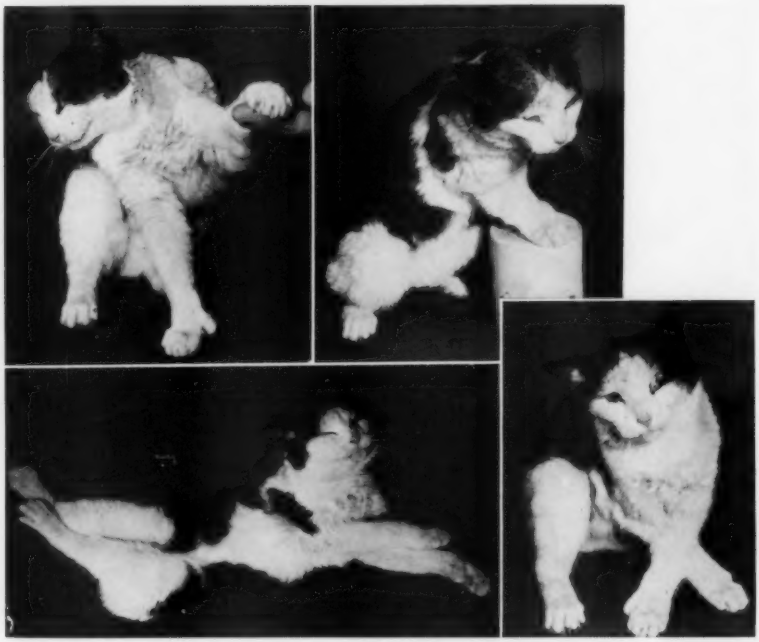


FIG. 4. (Cat P8-396) Catalepsy from a thalamic lesion. These attitudes were maintained for prolonged periods following ablation of the midportion of the mammillo-thalamic tract and intralaminar nuclei.

2c. *Unilateral and bilateral damage to the mammillary bodies and inferior portion of the mammillo-thalamic tract.*

Cat P8-395:

Lesion: A small subarachnoid hemorrhage had occurred in the interpeduncular space from one of the retromammillary arteries. The mammillary bodies and mammillothalamic tracts had been destroyed bilaterally, and a small hemorrhage had occurred in the left habenulo-peduncular tract (figure 3d).

Observations: During the first postoperative day decerebrate attacks occurred. Marked akinesis was present (figure 5b). Painful stimulation produced a withdrawal of all four limbs, and pinching of the gluteal muscles gave rise to running movements of the limbs. Lip-licking and salivation occurred in the blindfolded animal when fresh meat was held in front of its nose; this was interpreted as evidence of an intact olfactory sense. Persistent postoperative findings were a subnormal temperature of 95° F. (despite a warmed cage), bradycardia of 100 beats per minute, persistent extension of the claws on the right side, hyperactive deep reflexes and absence of hopping and placing reactions. Death occurred on the fourth postoperative day.

Cat P8-398:

Lesion: This discretely localized lesion involved only the right mammillo-thalamic tract, right mammillary body and adjoining fibres of the fornix (figure 3e).

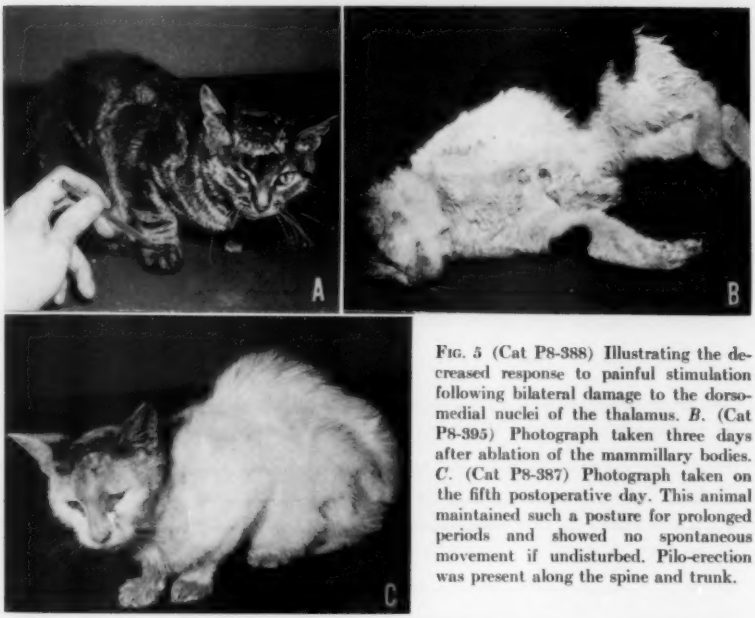


FIG. 5 (Cat P8-388) Illustrating the decreased response to painful stimulation following bilateral damage to the dorsomedial nuclei of the thalamus. *B.* (Cat P8-395) Photograph taken three days after ablation of the mammillary bodies. *C.* (Cat P8-387) Photograph taken on the fifth postoperative day. This animal maintained such a posture for prolonged periods and showed no spontaneous movement if undisturbed. Pilo-erection was present along the spine and trunk.

Observations: The thalamic electrodes were localized by the usual method of studying the responses to electrical stimulation (figure 1B, a). In this case, recordings were made from the cingulate gyrus on the side ipsilateral to stimulation. After the small rightsided lesion was made, the response disappeared (figure 1B, b). On raising the needle 2 mm. (into an undamaged portion of the mammillo-thalamic tract), excellent responses were again obtained. Immediately following this lesion, the electrocardiogram showed a marked slowing in rate. The animal lived for five days postoperatively. During this period it was markedly akinetic if left alone, but if stimulated it walked slowly in small circles to the right. Tube feeding was necessary. Many of the components of catotonia were present, abnormal postures being maintained for several minutes, while statuesque postures (as standing against the side of the cage) were assumed and maintained spontaneously. The right pupil was larger than the left. Persistent bradycardia (128 beats per minute) and a hyperthermia of 102° F. to 104° F. were noted. The claws were continually extruded on the right side. Hopping and placing reactions were intact. The cause of death on the fifth day was not determined.

Cat P8-400:

Lesion: The mammillary bodies were severely damaged bilaterally; the lesion also involved the junction of the mammillo-thalamic tract and the fornix with the mammillary body, together with the nucleus hypothalamicus posterior, all on the left side.

Observations: On the first postoperative day, the animal could not be aroused, although repeated painful stimulation produced slow withdrawal of the limbs. The pupils were equal and reacted to light, and the body temperature varied between 102° F. and 104° F. Piloerection was present on the back. On the second postoperative day,

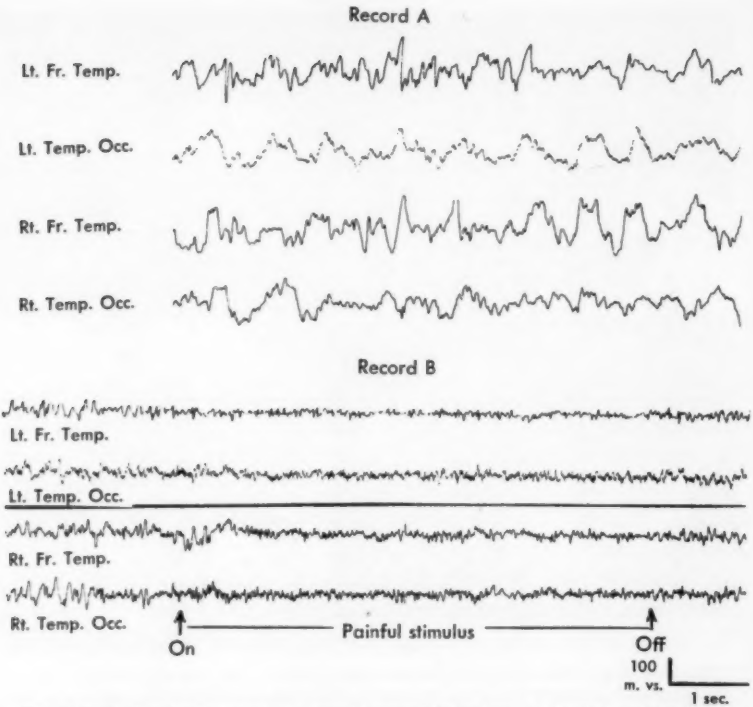


FIG. 6. Cortical excitatory state of a normal unanesthetised cat. *A*. Cortical activity during relaxation and apparent sleep. *B*. Cortical activity of the same animal during the relaxed waking state and when a painful stimulus is applied. Compare with stimulation in a postoperative animal.

the animal was found in a crouched position: the eyes were open and followed moving objects. Catalepsy was marked and together with akinesis remained constant until the fourth postoperative day on which the animal died after aspirating an intragastric feeding.

Electroencephalography of Group 2c. This group did not show marked changes between pre- and postoperative records; those observed consisted of random 2 to 4 per second slow waves from all head regions recorded.

3. *Group showing no marked change in behavior or electroencephalograms following operation despite extensive thalamic damage.*

Cat P7-99:

Lesion: damage to the midline nuclei; the nucleus reuniens was destroyed and there was involvement of the nucleus hypothalamicus dorsomedialis.

Cat P8-242:

Lesion: Principally bilateral destruction of the nucleus dorsal medialis.

Observations: There was no marked abnormality of behaviour except that response to painful stimuli was less manifest than in control animals.

Cat P8-354:

Lesion: Bilateral destruction of midline nuclei, stria medullaris and anterior portion of the nucleus lateralis.

Observation: No postoperative change in behaviour was detected.

Cat P8-369:

Lesion: Bilateral damage to the nucleus ventralis posteromedialis, intralaminar nuclei and habenulopedunclar tracts. The lesion bordered the mammillo-thalamic tracts medially without interrupting them.

Observations: The animal showed some decrease in activity following operation. Painful stimulation evoked little response. Gait was normal and although there was a tendency to maintain postures for prolonged periods of time, the animal could not be moulded into abnormal postures.

Cat P8-370:

Lesion: Bilateral damage to the nucleus lateralis pars posterior and intermedia and nucleus ventralis posterior. There was some damage to the left medial geniculate body and lateral pulvinar nuclei.

Observations: Apart from an exaggerated response to painful stimulation by scratching, hissing and biting, no behavior changes were observed.

Cat P8-388:

Lesion: Bilateral damage to the nuclei of the midline, nucleus dorsalis medialis, stria medullaris and the habenulopeduncular tract.

Observations: After operation the animal fed itself and walked about its cage. A markedly decreased response to painful stimulation was observed (figure 5a).

Monkey P8-408:

Lesion: Bilateral damage to the anterior limb of the internal capsule, caudate nucleus on the left side and anterior portion of the reticular nuclei of the thalamus. An interventricular hemorrhage was evident.

Observation: This animal lived for only one day postoperatively.

Electroencephalography of Group 3.

The postoperative recordings were not considered abnormal in this group.

DISCUSSION

The three control animals showed that the anesthesia, the attachment of the dural screw electrodes, the implantation of the electrodes into the diencephalon and the stimulation carried out for control placement do not cause, in our experience, either observable electroencephalographic abnormalities or change in behavior following operation.

Furthermore, comparison of the anatomical lesions in the group showing marked behavioral or electroencephalographic change with those in the group which showed little or no change following operation demonstrated that such changes are not dependent on a diffuse edematous reaction in the immediate postoperative period. It is possible, but as yet

remains unproven, that the localized thalamic lesions referred to may have produced localized changes in other structures by causing interference with the vascular supply at a thalamic level. However, the present study would indicate that the changes observed are more dependent on precise anatomical localization of the lesions.

Akinetic, apathetic states with thalamic lesions.

Of the group of nine cats with lesions in the region of the anterior nuclear group of the thalamus and upper end of the mammillo-thalamic tract, eight showed a markedly akinetic state and one animal (P8 379), although quiet following the operation, did not show the same degree of change as the other animals in this group.

Only three cats in this group could be classified as somnolent according to the observations of Kleitman.[24] For the most part the animals were not asleep but remained crouched without spontaneous movement and with their eyes open and following movements about them. They did not feed themselves, and if they were not fed they lost weight and died. They did not groom their coats which became matted and filthy and they showed no active interest in their environment. This state continued to be the most marked for the first 10 to 14 days, when there was some improvement and they began to feed themselves. However, there was a marked loss of initiative, of grooming, and of spontaneous movement which persisted for as long as the animal was studied.

The akinetic state appears from our evidence to arise from damage in the region of the upper end of the mammillo-thalamic tract and adjacent nuclear and fiber connections.

The similarity between the changes we have observed and those that Bailey and Davis[25] have previously described with lesions of the periaqueductal grey matter of the cat is indeed striking. Furthermore, the manner in which their animals frequently showed evidence of improvement after a few days but never complete return to normal function closely resembles the phases of recovery that have been noted on several occasions in the present series.

Akinetic state and catalepsy with thalamic lesions.

Both the cats with lesions in the region of the midportion of the mammillo-thalamic tract and intralaminar nuclei showed catalepsy and loss of spontaneous activity. Histological analysis of lesions in other animals which did not show catalepsy would tend to indicate in our experience that this group of symptoms is more dependent on damage in the region of the midportion of the mammillo-thalamic tract and neighboring fiber systems such as the periventricular fiber system than on damage to the intralaminar nuclear group per se.

Catatonia and unresponsiveness with lesions of the mammillary bodies.

In the two animals with bilateral lesions of the mammillary bodies, both animals were found to be profoundly unresponsive on the first postoperative day and could not be aroused. This persisted for four days in one animal until it died, although it could be propped up into cataleptic postures. In the other animal, the profound unresponsiveness was accompanied by catalepsy on the second postoperative day.

In one animal with a unilateral lesion confined to the right mammillary body and mammillo-thalamic tract, a definite tendency to maintain catatonic postures was present.

Such evidence would suggest that not only may catatonia in the cat arise from damage in the region of the mammillary bodies and mammillothalamic tract, but also that components of this syndrome may arise with a unilateral lesion in this region.

Although no anatomical studies have been made on monkey P8-412, the lesion is estimated to be in the region of the midportion of the mammillo-thalamic tract. Following this lesion there was some change in the animal's behavior. The animal became docile and stolid and lost emotional expression of the face. Although quiet, the animal has never been unconscious or hypersomnolent, although it appears abnormally drowsy at times and is seen to yawn frequently.

Electroencephalographic changes.

Most marked electroencephalographic changes were seen in the nine animals with lesions in the region of the upper end of the mammillothalamic tract and anterior nuclei of the thalamus. This change consisted in a generalized slowing of cortical activity similar to that sometimes seen in the normal, unanesthetized sleeping cat. The animals were not asleep, however, and when stimulated or given 0.5 cc. of Metrazol, there was some return of more rapid activity but there was never the same degree of general cortical excitation as was seen in the electroencephalogram of a normal sleeping cat when stimulated (figures 2 and 6). Furthermore, random slow activity between 1 and 4 cycles per second appeared regularly in the nembutalized record directly following the ablation.

It was thought at the beginning of this series that the degree of abnormal random slow activity observed in the first few hours postoperatively would serve as an index of the effectiveness of the lesions to give rise to a spontaneously inactive animal. However, it became apparent that this correlation did not exist and that frequently an animal with a very abnormal postoperative electroencephalogram could be quite active the following day. A similar lack of correlation was observed by

Kershman in a carefully analyzed series of human lobotomy cases.[26]

Changes in spontaneous cortical burst activity as observed in this series following the production of the lesions were of a minimal nature. In no instance was there an abolition of bursts from the cortex. In some experiments it was thought that following the lesions there had occurred an increase in the voltage of the spontaneous bursts, while in other cases the frequency of individual bursts appeared slower than that observed pre-operatively. The relative synchronization of bursts from one area to another appeared unaltered, while the interburst period in some instances seemed definitely lessened.

No conclusive abnormality could be discerned following ablation of the inferior portion of the mammillo-thalamic tract and the mammillary bodies, although some slow activity was occasionally seen.

In monkey P8-412, however, following a lesion estimated to be in the region of the midportion of the mammillo-thalamic tract, the post-operative unanasthetized record varied from normal alpha rhythm to delta activity depending on the state of the animal. Curiously, the alpha rhythm changed to delta activity with stimulation and the change persisted when the animal was struggling.

The electroencephalographic evidence would tend to suggest that there had been some interference with the sleep-waking mechanism following lesions in the region of the mammillo-thalamic tract, an interference which was more marked when there was damage in the region of its thalamic termination.

Autonomic Changes.

It was noted that lesions in the region of the midportion and upper mammillo-thalamic tract were almost invariably accompanied by a persistent tachycardia, by a temporary but nevertheless severe hyperthermia and by pilo-erection most marked along the trunk and back.

Lesions in the mammillary area gave rise to bradycardia and loss of temperature control varying from hypothermia to hyperthermia.

Other Observations.

It was noted that lesions of the dorsomedial nucleus gave rise to an absence of the normal response to painful stimuli.

In one animal with a bilateral lesion in the region of the anterior nuclear group of the thalamus, there was superficial erosion of the gastric mucosa. Since this was an isolated finding, its relation to the thalamic lesion remains undetermined.

One animal with a bilateral lesion involving the lateral thalamic nuclei showed an abnormally reactive response to painful stimuli, a re-

sponse which had not occurred prior to operation and which persisted for three weeks until the animal was sacrificed.

Since no studies were made involving lesions of the mesencephalon and rhombencephalon, the role they play in the abnormal states described could not be evaluated.

SUMMARY

Experimental studies in animals reveal that akinetic and apathetic states may be obtained with lesions in the region of the anteromedial thalamus and upper end of the mammillo-thalamic tract, and that these states are associated with electroencephalographic abnormality showing similarities to records obtained during sleep. Sensory stimulation, however, never produces the same degree of cortical excitation in these experimental animals as in the normal animal.

Akinetic and cataleptic states were produced in cats with lesions in the region of the midportion of the mammillo-thalamic tract, and symptoms of catalepsy and unresponsiveness were obtained by both unilateral and bilateral lesions in the region of the mammillary bodies and inferior portion of the mammillo-thalamic tract. Spontaneous electroencephalographic changes were not marked in this group.

CONCLUSION

The effects produced by localized coagulations of the diencephalon in cats suggest that regions in the vicinity of the mammillo-thalamic tract and adjacent structures play an important part in the mechanism of responsiveness in animals.

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Many attempts have been made to *localize* the functions of the cerebrum; that is, to prove certain functions to be attached to certain parts of that organ; without, however, much success. The facts supplied by pathology certainly lead us to the conclusion that the hemispheres of the cerebrum and cerebellum regulate the *voluntary* movements of the *opposite* side of the body; whilst the medulla oblongata and spinalis *convey* these acts of *volition* to the *corresponding* side.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

Relief of Pain in Trigeminal Neuralgia By Crystalline Vitamin B_{12}

William S. Fields, M.D. and Hebbel E. Hoff, M.D.

Relief of neuropathy in pernicious anemia by the administration of small doses (15 to 30 micrograms) of vitamin B_{12} has suggested its employment in the treatment of nervous disorders of unknown etiology. Reports that the substance is of value in the relief of pain of alcoholic and diabetic neuropathy as well as in peripheral neuritides of non-specific origin have led to its employment in the treatment of other painful states. Despite statements that B_{12} failed to alleviate the pain of trigeminal neuralgia when employed in the conventional dosage, the recent availability of a solution of far greater potency permitted the hope that greater doses might prove effective.

Since May 1950, 13 cases of trigeminal neuralgia have been treated. The first six patients were given 1000 microgram doses biweekly or triweekly for periods of four to eight weeks. In all instances the pain was markedly relieved within the first week, usually after the second injection. In four patients the sharp lancinating type of pain gave way to a more or less burning paresthesia in the same area which was not aggravated by stimulation in the trigger zone and did not radiate. This latter sensation disappeared in all cases with continuance of therapy, although it was more resistant to treatment.

In two cases shortage of the material made it necessary to discontinue therapy for approximately one week shortly after the typical attacks had ceased, but while the burning sensation was still present. In both cases the lancinating pain returned, but was relieved after the first of six daily injections of 1000 micrograms each. Because of the return of symptoms when therapy was interrupted and because of the more resistant burning sensations, it was decided to give daily injections over a ten-day period in an attempt to maintain a more constant therapeutic level. The last

From the departments of neuropsychiatry and physiology, Baylor University College of Medicine, Houston, Texas.

seven cases in this series have been thus treated. The relief was equally prompt in the first of these, and burning sensations did not occur. In one case the patient was extremely obese and intramuscular injection in the gluteal region was difficult. Considerable pain remained on the eighth day, although there had been reduction in the frequency of the paroxysms. Intradeltoid injections gave complete relief and suggested that the first dosage had been ineffective because of interference with absorption by the subcutaneous fat in the buttock.

The first patient treated has now had no recurrence of pain in the eleven months elapsing since the last injection. The second patient treated has remained free of pain for 10 months since discontinuation of therapy. Others have had relief for lesser periods, but at the time of this report there have been no recurrences in this series. None of these patients has requested other therapy.

Five of the patients in this series (cases 1, 4, 5, 7 and 10) had received other therapy in the past. Two of them (cases 5 and 10) had undergone nerve section on one side with subsequent recurrence of pain in the opposite trigeminal distribution. In the other three cases there had been repeated alcohol blocks with eventual relapse and increasing reluctance on the part of the patient to undergo further surgical intervention. Four of these (cases 4, 5, 7 and 10) proved to be the most resistant patients in the series, but the ultimate degree of relief was the same.

SUMMARY OF CASES

Case 1.—A man aged 49 was first seen on May 4, 1950. He gave a history of the onset, in October 1943, of a sharp lancinating pain beginning near the left corner of the mouth and radiating posteriorly to the angle of the jaw. The pain occasionally radiated to his left cheek, accompanied by increased lacrimation of the left eye. The paroxysms were of brief duration, lasting from a few seconds to 30 or 40 seconds. There was a trigger zone on both inner and outer margins of the lower lip on the left. Episodes of pain were often brought on by a cold wind striking the face or by the drinking of cold liquids. The first bout of pain lasted about six months, and during this time there was no relief from medication. The pain returned in 1946 and after four months the patient received an alcohol injection of the mandibular division which gave complete relief for about eight months. The pain returned with greater severity even before the anesthesia resulting from the injection had completely disappeared. This series of attacks lasted for about 18 months. The present bout of pain started in December 1949. The patient received nicotinic acid without relief. He was occasionally able to reduce the severity by the inhalation of tetrachlorethylene. Neurologic examination at the time of the first visit in May 1950 was entirely negative. He was started on B_{12}, 1000 micrograms three times weekly for two weeks, following which the dose was reduced to twice weekly for two weeks, and then once a week for the ensuing five weeks. Following the second injection, there was no further lancinating pain. When last heard from in November 1950, there had been no recurrence of pain.

Case 2.—A woman aged 67 was first seen on May 30, 1950, when she gave a history of episodes of pain in the right side of the face for the past fourteen years. There was a trigger point on the tip of the nose. She also had noted that drinking fluids or combing her hair over the right side of the forehead would precipitate a paroxysm. The patient carefully avoided touching or washing the right side of her face to avoid precipitating attacks. This patient would be free of pain for several years at a time; when pain reappeared, it persisted from two months to nearly two years. The pain was largely confined to the right cheek, but it occasionally spread to the right eye and over the right side of the forehead. She had received no previous treatment at any time other than analgesics or narcotics. She was started on B_{12}, 1000 micrograms three times weekly for two weeks, twice a week for two weeks, and then weekly for the ensuing four weeks. She had less pain after the first injection and no pain after the second injection. There was a slight residual burning in the right cheek for four or five days. There had been no recurrence of pain when the patient was last seen in late December 1950.

Case 3.—A man aged 39 was first seen on October 9, 1950, complaining of a severe intermittent pain in the left side of the face of approximately six weeks duration. This pain had a sudden onset near the angle of the left mandible and radiated sharply toward the left ear. Shortly after the onset of the pain the patient visited his dentist and four teeth were extracted in that area, without relief of the pain. The spasmodic paroxysmal pain was brought on by movement of the tongue or presence of food in the mouth, and because of this the patient gradually restricted his diet until at the time of the first visit he was living on milk, lukewarm soup and warm coffee. Hot or extremely cold liquids precipitated attacks. Because of the restriction in his diet the patient had lost almost 30 pounds in one month. He was placed on vitamin B_{12}, 1000 micrograms intramuscularly three times weekly. Approximately two hours after the first dose of this medication the patient reported that he was able to eat a complete meal for the first time in five weeks. Thereafter he was given a single weekly injection of vitamin B_{12} in the same dose. Eight weeks after the beginning of this therapy the patient had a mild recurrence of the paroxysmal lancinating pain, and at that time he was readmitted to the hospital and given a course of ten daily injections of 1000 micrograms with complete relief. When last heard from on April 9, 1951, the patient stated that he had had no recurrence of pain.

Case 4.—A woman aged 69 was first seen on November 22, 1950, when she gave a history of onset of pain in the right side of the face ten years previously. This pain had been intermittent in that she did have remissions of one to two months during that time. Three years prior to her first visit she had received an alcohol injection of the second division of the right trigeminal nerve, following which she had a six months period of relief from pain. This patient was started on B_{12} three times weekly in 1000 microgram doses. After the second injection she had no further attacks of pain, but complained at the time of her third injection that there was still a little burning on the right side of her nose, extending up into the supraorbital region. This persisted for another four or five days. This patient received three injections weekly for two weeks, and two injections weekly for two weeks. At the end of this time, she had no further discomfort, and at last report (five months after first visit) there was no recurrence.

Case 5.—A woman aged 71 was first seen on November 24, 1950, when she gave a history of onset of pain on the left side of the face 18 years previously. There was a trigger zone on the left side of the nose. About two years after the onset of pain the patient had an alcohol block of the left maxillary division. The relief from pain and the anesthesia

lasted for about six months. Following this the pain returned with increased severity, and in 1938 she had a retro-gasserian section of the left trigeminal nerve which gave complete relief. One week prior to her visit, the patient first noted a pain of similar character which began on the right side of her nose. This pain radiated upward into the supraorbital branch of the first division on the right side. Since, in addition to the permanent anesthesia on the left side, there was also some weakness of the motor division of the left fifth nerve manifested by weakness of the muscles of mastication, it appeared most urgent that medical therapy be tried to forestall bilateral surgery. This patient was given B_{12} three times weekly in 1000 microgram doses, and after the second injection she had begun to notice some improvement in that the severity and frequency of the attacks had lessened. During the second week, the therapy had to be interrupted because of a shortage of supply of the injection material, and the patient had a return of the sharp pain in the right side of her face. She then received a similar dose every other day for the next two weeks. On January 6, after a total of 15 injections, there was almost complete relief. Then, because of a shortage of the material for injection, there followed a period of one week during which therapy had to be interrupted. At the end of this week the pain had again returned, although not as severe as before treatment was started. The roof of the mouth was still a trigger zone. She was given 6 ampules for daily injection, and following this period of more frequent treatment she was completely relieved of pain for three weeks. Pain returned in lesser intensity three weeks later and was again relieved by a series of nine injections. When last seen on April 19, 1951, there had been no return of pain.

Case 6.—A woman aged 74, who was first seen on January 8, 1951, gave a history of left facial pain in which the first attack occurred 19 years ago. This episode lasted for about three months. The patient remained entirely free of pain for 15 years when it returned, somewhat less severe than during the first bout. Again, it lasted for about three or four months. In December 1950 the pain returned and this attack was far worse than either of the previous ones. The pain was sharp like "a lightning spasm." There was a trigger zone about 2 cm. in diameter at the lower left corner of the mouth. The patient was afraid to open her mouth wide in order to eat or speak, and had been unable to take more than a little liquid for several weeks. She had also found that a cold wind would often precipitate a paroxysm. Her sleep had been markedly interfered with, but she had taken only aspirin or empirin compound with almost no relief. She was started on B_{12}, 1000 micrograms daily, and following the third injection was completely relieved of her pain. In this instance, no burning paresthesia remained. She was continued for a total of eleven doses, after which therapy was stopped, and on last report three months later had had no return of pain.

Case 7.—A woman aged 90, when first seen on January 11, 1951, gave a history of the onset of pain in the right side of the face beginning about four years previously. This series of attacks lasted for about three to four months and was not very severe, but it was quite typical of trigeminal neuralgia, and was frequently precipitated by speaking and by eating. Following a spontaneous remission of the pain, she was entirely free until three years later when it suddenly returned with marked increase in severity. After about two weeks an alcohol block of the second division on the right side was performed with complete relief for about 11 months. In December 1950 she had a return of pain, this attack being similar to the ones she had experienced one year before. This patient, like the previous ones, received 1000 micrograms daily and had some relief after

the third injection. At this time she went about 48 hours without a single paroxysm. After eight daily injections, the patient was still having occasional paroxysmal, lancinating pains, some of which were quite severe. However, they were much less frequent and most of them were of a shorter duration. This patient was extremely obese, weighing over 200 pounds. It was not certain whether the injections which were intended to be intramuscular actually were made into the muscle, or into the overlying fat, and accordingly a series of 10 injections was made into the deltoid with complete relief. By April 16 there had been no recurrence for nine weeks.

Case 8.—A woman aged 50 was admitted to the hospital September 23, 1950 with a complaint of pain in the right face for about two years, occurring in an intermittent series of attacks. Her most recent episode started about six weeks prior to admission following wide opening of her mouth to yawn. The pain was sharp and lancinating, beginning near the angle of the mouth on the right side, and radiating backward to the angle of the jaw, and then referred to the right side of the forehead on some occasions. For several days prior to admission the patient had been inhaling trichlorethylene during the attacks, and this had given her relief for a few hours. There was a trigger zone on the outer margin of the lip near the right corner of the mouth, and touching this area would evoke an exquisite paroxysm of the pain in the distribution described above. The blood Kolmer-Wassermann was 3 plus, and the patient stated that she had had a course of antisyphilitic therapy about three years previously. Examination of the spinal fluid was entirely within normal limits. On October 2, 1950 the patient was given her first injection of 1000 micrograms of vitamin B_{12}. Eighteen hours later she could talk with greater ease, was able to eat her meals without pain, and could touch the right side of her mouth without eliciting a paroxysm. She received a second injection on October 4th with continued improvement, and by the 5th of October had only an occasional vague burning sensation in the lower right half of the face. A third injection was given on October 6, and the patient remained asymptomatic until her discharge on October 13. She returned to the outpatient clinic on October 21, complaining that there had been a mild recurrence of pain two days before. She was given one additional injection of 1000 micrograms, and at last report about February 1951, she was still asymptomatic.

Case 9.—A man aged 45 was first seen on January 18, 1951. He gave a history of onset of pain in the face at the age of 18. This pain began above the inner canthus of the left eye, and seemed to radiate into the orbit and up over the scalp to the vertex of the head. Occasionally the skin on his face felt somewhat peculiar. There was also a peculiar sensation in the hair over the left anterior part of the scalp. In 1945 the patient had an operation on the left middle turbinate, and it was found at that time that an attack of the pain could be relieved by cocainization of the nose in that region. This patient had a serious bout of pain beginning in July 1950, when paroxysms occurred frequently over a period of seven weeks. The patient thought that an attack might be precipitated by eyestrain, and frequently a paroxysm was brought on by exposure of the left side of his face to a cold blast of air. The paroxysms often occurred during his sleep and would awaken him. They were of variable duration and intensity. His present attack had begun about two months previously, and he had had paroxysms as often as five or six times a day. The pain was not relieved by any medication, including narcotics. There was a marked sensitivity to tactile stimulation over the forehead and eyebrow on the left side, and a sensitivity in the hair over the left anterior scalp. A paroxysm of pain could be elicited by stimulation of the mucous membrane of the nose just inside the lateral aspect

of the left nostril. The patient was immediately started on vitamin B_{12}, 1000 micrograms daily. He did not receive the dose on the second day, but received daily injections thereafter for a total of six injections in seven days. Following the fourth injection he had a sudden disappearance of the pain and it had not recurred when he was last heard from on April 17, 1951.

Case 10.—A woman aged 78 was first seen on February 24, 1951. There was a history of the onset of acute paroxysmal pain in the left corner of the mouth some 23 years previously. This pain radiated along the lower jaw toward the left ear, was extremely severe, and was not relieved by any therapeutic measures attempted at that time. Two years after the onset of the pain the patient had the first of several alcohol injections in the third division of the left trigeminal nerve. The pain was relieved on each of these occasions for approximately six or seven months. In 1946 the patient underwent post-ganglionic section of the left trigeminal nerve, which completely relieved her pain and left her with a permanent analgesia in the left side of the face. About six months after this operation, the patient first noted a severe pain which occurred intermittently in the tip of the tongue on the right side. This pain came in attacks every few months and occurred in paroxysms about 10 or 12 times a day. Her last attack began four months prior to her first visit. The pain had gradually increased in frequency and severity. The patient noted that touching the left side of her jaw below the corner of the mouth would precipitate a sudden paroxysm of pain beginning in the right side of the tongue which would radiate along the floor of her mouth and along the lower jaw to the right ear. This pain could also be precipitated by talking and by eating. Therapy was instituted with 1000 micrograms of vitamin B_{12} daily, injected intramuscularly, and after the third day the shooting pain had disappeared, leaving a burning pain restricted to an area on the right tip of the tongue about 1 centimeter in diameter. This pain did not restrict the patient's activity, and she began to eat and gain weight, to talk and laugh freely, activities which hitherto had been impossible. Because of the persistence of the burning type of pain, therapy was continued for 16 days, at which time daily injections were discontinued, although the burning sensation and small non-spreading attacks still occurred at the tip of the tongue. She was placed on weekly injections and three days after the second of these injections she became completely free from pain and at the present time has been free from pain for two weeks.

Case 11.—A woman aged 62 was first seen on March 14, 1951, presenting a history of intermittent attacks of pain in the right side of the face during the previous 10 years. Pain has been absent at times for a period as long as one year. During the month previous to her visit she had experienced the most severe bout which she had yet suffered. The paroxysms occurred at least 20 or 25 times a day and lasted from 10 to 15 seconds. There was occasionally a residual burning lasting a minute or two. A trigger zone was present on the right upper lip near the angle of the nose. The pain radiated posteriorly toward the right ear and up into the right supraorbital region. Increased lacrimation in the right eye accompanied the pain. The patient was immediately started on daily intramuscular injections of 1000 micrograms of vitamin B_{12}, and on the evening of the second dose she felt much better and slept the entire night without medication. The pain changed its character to the burning type of pain described by other patients. During the next 10 days while daily injections were given, the patient had occasional pain but usually only of a burning kind and never a full-blown radiating attack. After 14 daily doses, weekly injections were begun and after two of these the relief was so

complete that the patient voluntarily decided not to have any further injections. On April 23 there remained some periods of burning pain.

Case 12.—A woman aged 89 gave a history of pain in the right side of the face starting in 1948 with an attack lasting approximately three weeks. Since that time there had been long periods of remission but also periods of paroxysms of pain lasting several months at a time. The most recent attack began in October 1950, and has lasted without remission up until the time of her first visit on March 17, 1951. There were trigger zones on the right side of the face in the naso-labial fold and also at the inner canthus of the right eye. The pain was frequently precipitated by chewing movements of the jaws with the result that the patient had severely restricted her diet. She had never received any treatment other than aspirin. Therapy was immediately begun with daily injections of 1000 micrograms of vitamin B_{12}. By the fourth day practically all of the pain had been relieved and the patient was able to eat her meals without discomfort. Therapy was continued for 10 daily injections and an additional single injection given one week after the termination of the daily therapy. There had been no recurrence when the patient reported some two weeks after discontinuation of therapy. On April 24, however, the patient reported some return of typical attacks, and therapy was initiated again.

Case 13.—A woman aged 61 was first seen on March 27, 1951, when she stated that she had had an onset of pain in the right side of the face in 1947. This pain radiated posteriorly into the right cheek and occasionally upward into the right side of the forehead. There was a trigger zone in the naso-labial fold on the right side. In four years' time the patient had never had more than a few days' remission. Her most severe attack began about 10 days before her first visit. She was unable to eat and did not dare wash or touch her face on the right side. There were severe paroxysms of lancinating pain which extended chiefly into the supraorbital region on the right and occasionally posteriorly toward the ear. She had never received medical treatment until five days previous to her visit, when her private physician gave her some codeine tablets, which did not afford her any great amount of relief. The patient was started on daily injections of 1000 micrograms of vitamin B_{12} intramuscularly. By the third day she was completely relieved of the sharp paroxysmal type of pain whereas the mild residual burning above the right eye persisted for about two days longer. Therapy was discontinued on the tenth day and one month following termination of treatment she reported that there had been no recurrence.

DISCUSSION

The history of the medical treatment of trigeminal neuralgia leads one to approach with caution the evaluation of a new method. Yet after a year of experience with the use of massive doses of vitamin B_{12} it is felt that this substance offers promise of prompt relief of the most distressing aspects of the pain, with ultimate complete or virtually complete relief of the secondary burning paresthesia. The early relief of paroxysms has made a profound impression upon all of the patients studied in the series. The residual pain is bearable, fearful anticipation of further attacks is diminished, and the reaction to return of paroxysmal pain has been favor-

able because of confidence that resumption of therapy will again cause the worst of the pain to disappear.

It has been obvious that complete relief has been more difficult to achieve in those patients in whom previous surgery, as by neurectomy or by alcohol block, has been undertaken. This may be a manifestation of the severity of the fundamental processes involved in the disease, and its duration, for on the average those patients who have had repeated recourse to surgery will be those who have suffered the most severely and for the longest time. It is undeniable also that with increasing severity and duration the psychologic associations become more firmly ingrained and may serve to maintain a painful state at central rather than peripheral loci. Whatever the factors may be that make the extensively treated case more resistant to therapy, there is no doubt that ultimately these patients show equally complete relief.

Perhaps the best evidence of the success of the present therapy is afforded by the subsequent behavior of the patients in this series. None has asked for other relief such as injection, surgery or other medication, and even those who continued to show persistent pain of a lesser degree or of a changed character indicated their relief by the freedom with which they talked, smiled, and otherwise employed their facial musculature in the expression of feeling. This progressive thawing of the typical frozen facial expression of the patient with trigeminal neuralgia was often more expressive than their verbal reports of improvement.

It is clear from the course of events following therapy that the end results have been produced by therapy and do not represent the fortuitous onset of the spontaneous remissions which practically all patients have experienced in the past. It is equally understandable that the effect of therapy may have been restricted to bringing on a remission without in any sense producing a fundamental cure of the disease. There is nothing to indicate, however, that if and when attacks again make their appearance, further therapy of the same kind will not again be equally effective.

The separation of the recovery period in almost all patients into stages of early relief of paroxysmal pain and later relief of slow burning pain calls attention to the double character of the pain that escapes notice in most untreated cases, though its existence can often be verified by direct questioning, as in case 11. Similar differentiation of sharp and burning pain has been made in states of causalgia and phantom limb pain, and offers clues to the fibers involved, or to the pathogenesis of the conditions which elude elucidation at present.

What is now known of the functions of vitamin B_{12} in nerve metabolism indicates that dosage employed in these studies is far above minimum

physiologic requirements, and the effect of therapy is not to be explained on a simple replacement basis. It is to be hoped that continuing studies of the role of B_{12} in the neurone will in the future shed light on the pathogenesis of trigeminal neuralgia. The beneficial effect of this vitamin in trigeminal neuralgia as well as in other peripheral neuropathies suggests a common factor in their pathogenesis, despite the obvious differences of causation, localization and clinical course.

The success thus far achieved in the treatment of facial pain with vitamin B_{12} suggests that this treatment be employed as that of first choice, and that attention be given to its value when administered as early as possible in the development of the disease.

SUMMARY

1. Thirteen cases of trigeminal neuralgia have been treated with large doses of vitamin B_{12} administered intramuscularly.

2. Remarkable relief was obtained in all cases, with prompt and complete remission in nine cases.

3. All of the nine cases completely relieved had not had previous surgical intervention.

4. In four cases where surgery and nerve block had been resorted to, relief from pain was delayed, although ultimately results appeared to be equally good.

Nothing has hitherto been done to subject the human brain to a course of experiment in order to determine the nature of its functions. It is true lesions have occurred so exactly limited to special parts as to throw great light on their uses. In this way the faculty of language has been associated with the anterior part of the left hemisphere, the corpora striata with motilily, the optic thalami with sensation, etc. The influence of pressure has been studied in cases of injury, hemorrhagic extravasation, effusion, etc. The brain when exposed by injury has experienced such a degree of concussion or damage to its structure, that any exact observations of the functions of its parts cannot be made. Having had a case recently in which a considerable portion of the posterior lobes of the brain was exposed by disease without any interruption of its functions, I ventured to make some experiments on the plan pursued by Fritsch and Hitzig and Ferrier.

—Roberts Bartholow in *Experimental Investigations into the Functions of the Human Brain*, published in 1874.

On Certain Aspects of the Sensory Organization of the Human Brain

III. A Patterned Response to Three Simultaneously Applied Cutaneous Stimuli

Robert Cohn, M.D.

During sensory examinations in which several simultaneous stimuli were applied to cutaneous areas to determine rostral and lateral dominance, an interesting pattern of organization was recognized.[1, 2] When the stimuli* were three in number, one on the lateral surface of the face and the other two applied to the dorsum of each hand or wrist, the general perceptual response was recognition of the face and the contralateral hand stimuli. The stimulus on the ipsilateral hand was usually unrecognized. In a similar way, again using three simultaneous stimuli, if one was placed on the dorsum of the hand and the other two at the ankles or feet, the hand stimulus and the contralateral foot stimulus was ordinarily reported. The perception of the ipsilateral distal stimulus was usually unrecognized.

This phenomenon was seen in a large number of neurologically intact subjects. At times the crossed response was elicited only on the first patterned stimulation, and all remaining sets of stimulation were completely and accurately resolved. In individuals with decreased sentiency due to brain cell damage resulting from arteriosclerosis, syphilis and space taking lesions the crossed response persisted indefinitely. Some of these latter patients persisted in the crossed response even when the stimuli were applied as many as 30 times. A similar but less intense response was also seen in certain patients under the influence of sodium Amytal. Contrarily, patients who appeared under marked psychic tension or stress seldom failed to resolve the applied multiple stimuli even on

*Tactile stimuli were used throughout. The intensity and localization of the areas of stimulation were not critical, although light, rapidly applied stimuli resulted in more frequent obliteration responses than when the stimuli were slowly and heavily applied.

From the U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland.

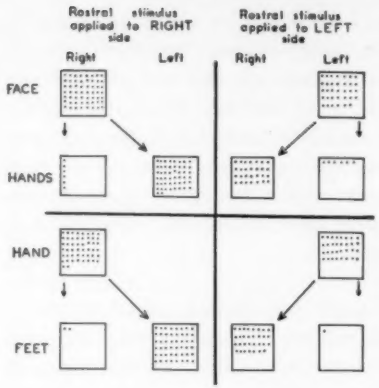

FIG. 1. *(left)* Data compiled from a consecutive series of patients who showed obliteration of either the contralateral or ipsilateral caudal stimulus. Each dot indicates the perception of the applied tactile stimulus. The predominance of the perception of contralateral stimuli is striking.

the first application. In somewhat less than one-seventh of this entire series of cases, the patient would designate the rostrally applied site of stimulus and the ipsilateral more distal (or caudal) position, thereby obliterating the contralateral stimulus.

Figure 1 presents the data obtained in a consecutive series of neurologically normal patients who were in entirely appropriate interpersonal contact at the time of testing. If a patient resolved all three stimuli in the first set the experiment was considered negative and no marks were placed in the squares. This resolved response occurred approximately in one of every six patients. When the patient was stimulated on the left face and each hand and reported the left face and the right hand, a dot was placed in the left face square and the right hand square. If the right hand and each ankle were stimulated simultaneously and the right hand and right ankle were reported, then the dots were placed in the appropriate squares. At first, care was taken not to alert the patient to the multiple testing, but to carry out the triple simultaneous stimulation as part of the general sensory examination. Later is was noted that this precaution was not necessary. If it happened that a patient showed repeated crossed responses, then four stimuli were applied simultaneously, over each face and each hand; in these instances all the normal individuals designated all four places of contact and from then on would usually resolve the repeated triple stimuli. In certain of these patients, however, if single stimuli were again presented and then multiple stimuli were reapplied they sometimes again gave crossed responses (i.e., obliterated the ipsilateral distal stimulus). Of course, as observed in ordinary rostral dominance,[2] if the stimulus pattern was each lateral surface of the face and one hand, then only the face stimuli were reported.

In certain patients one hip versus both knees or ankles gave rise to crossed responses just as in the more easily applied face-hand stimuli. Throughout, the rostral (or proximal) dominance was in good conformance with that observed and reported in ipsilateral paired stimuli.[2]

In this present work some corrections for the data had to be employed as several subjects felt that the ipsilateral stimulus was so light that they believed it was a chance contact and consequently reported only the crossed stimuli. Such responses were then considered negative. Following such reports the examiner took care to ask if any stimuli other than that reported was perceived. Another source of error in the earlier test series was that several patients could not, at first, appreciate that three stimuli could be applied simultaneously. Therefore, they only reported two points of contact. The results obtained in these individuals were not included in this study. Despite careful testing, children in general became confused by the multiple stimuli, and no definite pattern of response resulted.

The crossed pattern of response appeared to be compatible with the phenomenon of "specific overlap" as formulated by Wade H. Marshall and coworkers.[3] This effect took into consideration that when the primary cortical face area was activated by proper cutaneous stimuli parts of the adjacent hand area too were excited. If such physiologic action can be directly correlated with the clinical behavior in man, it would seem that the two ipsilateral stimuli must compete with each other for specific primary cortical neurons in the process of perception of cutaneous stimuli. The contralateral stimulus, although it is applied to caudal (or distal) part, has no competition for the specific neuron pool necessary for perception of the tactile stimulus. On the basis of this hypothesis tests were formulated and executed to determine whether simultaneous stimulation of topographically distant cortical areas would show a different response than simultaneous stimulation of cutaneous regions that had adjacent cortical representation. In more than 100 patients the response to face-hands was compared with the response to face-feet. Approximately one-third of the patients who showed positive crossed (ipsilateral obliteration) responses in face-hands and hand-feet stimulation demonstrated a resolution (recognition of all three stimuli) in face-feet stimulation. It must be emphasized that this latter phenomenon (resolution of face and feet stimuli) occurred while the ipsilateral obliteration of face-hands or hand-feet stimuli were still elicitable in successive testing. The result of this type of clinical examination demonstrated that specific overlap in the primary sensory areas, although apparently important, were not solely responsible for the observed phenomena. Consequently it became necessary to further

postulate that higher level integration and organization played a significant role in determining the observed responses.

The occasional finding of obliteration of the contralateral stimulus in certain subjects appeared to be part of a "confusion" in that subsequent stimuli resulted in the extinction of the ipsilateral stimulus. However, in other subjects the contralateral stimulus was repeatedly obliterated and one can only assume that the perceptual organization of the brains of these individuals was different than the majority of patients studied.

CONCLUSION

Three tactile stimuli when simultaneously applied, one rostral to two homologous more caudal (or distal) parts, result in the obliteration of the stimulus from the ipsilateral caudal part in the great majority of patients studied.

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We know little of the way in which pain in the head is produced. The brain of an animal can be cut or torn without the creature showing signs of suffering. But the significance of this fact may be over-rated, since other structures, that seem normally insensitive, become acutely painful when diseased. It is certain, however, that the membranes are very sensitive and highly probable that much of the pain of intracranial disease is produced in them. Some diseases, as tumor, have been thought to cause pain by the pressure they produce, but the evidence that this is commonly the effective mechanism is insufficient, since other diseases may increase the intracranial pressure, locally and generally, without causing pain. Nor can we reasonably invoke the ready explanation of "congestion" as a universal mechanism; in many conditions of headache this is out of the question. In short, until we know more than we do at present, speculations as to the way in which headache is produced are scarcely profitable.

—Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Psychologic Tests in the Diagnosis of Organic Brain Disease

Edward D. Hoedemaker, M.D. and M. E. Miriam Murray, M.S.

THE ROUTINE examination of adults coming to a neurologic and psychiatric clinic for diagnostic study and treatment has revealed considerable variation in the sensitivity of the procedures used in such examinations. Striking variations have been noted in the study of individuals where the presence of organic brain disease has been suspected. In a group practice devoted to the diagnosis and treatment of both psychiatric and neurologic disorders, the majority of patients are psychiatric. With available psychotherapy varying from simple counseling to orthodox psychoanalysis, it is of primary importance to determine the presence or absence of organic brain disease, bearing in mind that deeper, more intensive psychotherapy is often contraindicated or requires considerable modification in individuals with damaged brains.

The problem, then, has become one which has to do with the detection of brain damage, whether old or recent, acute or chronic, active or inactive, focal or diffuse. It has come to our attention that frequently some of the common diagnostic procedures have failed to show the presence of organic brain disease at a time when a battery of psychologic tests showed "organic" findings. It was decided, therefore, to study the records of a series of adults who were suspected of having organic brain disease, such suspicion being the result of the intake examination and history taking, the neurologic examination, or when "organic" evidence appeared in the results obtained by the clinical psychologist in the administration of a battery of psychologic tests.

REVIEW OF THE LITERATURE

The literature of psychologic testing contains many studies correlating the indications of organic brain pathology in single psychologic tests

From the departments of neurology and psychology, Northwest Clinic of Psychiatry and Neurology, Seattle, Washington.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 13, 1951.

with validating procedures in the neurologic field. A few studies have compared the interrelated findings of several applicable psychologic tests with one or several neurologic procedures, but a comparative study using a battery of psychologic tests against neurologic procedures has not been reported previously.

Diagnostic accuracy is more nearly approached by the cross-reference system of studying pathology, near-pathology or contraindication to pathology by using a battery of psychologic tests chosen to supplement each other. In this way, the clinical psychologist does not depend upon "organic signs" or their absence in any single test in the detection of evidence of organic brain pathology. The sign pertaining to certain major areas of central nervous system functioning have been investigated and published in the literature which acknowledges the lack of clear-cut boundaries between each of these areas mentioned and also acknowledges their essential interrelatedness.

At the risk of oversimplification, six major areas of central nervous system functioning have been chosen arbitrarily for the present study. These areas are: memory, thinking processes, perception, affect, speech and motor functions. It is assumed that the signs for organic disease have been sufficiently investigated in individual tests.[1-11] It is proposed to use these data in the study of individuals with organic brain disease.

In the neurologic literature, some studies have appeared which compare the sensitivity of psychologic tests with other findings in the diagnosis of organic brain disease. Koff[12] found considerable correlation between increased spinal fluid protein and "organic" response on the Rorschach test, and felt that the Rorschach test was helpful as a differential diagnostic aid among casualties in forward areas of combat. Greenblatt, Levin and Atwell,[13] using the Goldstein modification of Koh's block design, the Weigle form color sorting, the color sorting with the Holmgren yarn, and the Shipley abstraction test, studied 39 cases of organic brain disease as well as a series of controls, and concluded that the abstraction tests gave evidence of organic brain disease in 59 per cent of the cases. They found the electroencephalogram abnormal in 44 per cent of these cases.

The use of a battery of psychologic tests for purposes of diagnosis, prognosis and personality evaluation is an accepted correlative function of clinical procedure in pyschiatric clinics. The purpose of this paper is to demonstrate its value in the detection of organic brain disease as well. Needless to say, any diagnostic tool having a higher degree of accuracy than routine methods now in use for the detection of organic brain disease would be of great value to practicing neurologists and psychiatrists.

By way of review, the selection process of a battery of psychologic tests

for clinical use, the relationship of each test to the total battery and to the other tests of the battery, have been discussed by previous authors.[9] The continued use of such a battery increases the refinement of the test data, serves to discover new areas of sensitivity of the battery, and systematically increases the diagnostic skill of the psychologist employing it. The sensitivity of psychologic test results of any given test battery depends not only on the particular group of tests used but also on the acuity and skill of the user. A framework of familiarity with psychologic disorders, their syndromes and dynamics, with or without neurologic disorder, as well as with the behavior of so-called normal adults and children is a necessary prerequisite for interpreting test results. This particular battery of tests has been in use in the examination of adults and older adolescents in this clinic for over four years. It has been used in conjunction with social histories obtained by psychiatric social workers, psychiatric examinations performed by psychiatrists, and neurologic examinations performed by a neurologist, whenever these various procedures have appeared necessary to fully understand the patient's problem.

The psychologic test battery used in this study is composed of 1) the Wechsler-Bellevue Intelligence scale for adults; 2) the Rorschach diagnostic personality test; 3) the B.R.L. sorting test; 4) a word association test; 5) the Ellis visual designs test; and 6) the Szondi test. As has been mentioned above, various of these tests and other single tests or groups of tests have been reported in other studies to show their relative degree of diagnostic sensitivity in the detection of organic brain disease validated against criteria such as electroencephalographic findings, general neurologic examinations, etc., but this study presents for the first time an exploration of sensitivity of a battery of tests to the presence of organic brain disease as compared with other diagnostic procedures. It is to be emphasized that the repeated use of the same battery of tests aids the clinical psychologist in increasing his awareness and acuity in detecting the obvious, less obvious and the more obscure pathologic processes. It is an accepted fact that no one test can be a complete diagnostic tool in itself for any or all psychologic disorders, for each varies from case to case and from group to group, and in sensitivity from psychologist to psychologist.

Diagnostic accuracy is not increased by increasing the number of tests employed unless the added tests are known to select information to supplement the findings of the other tests of personality functioning at different levels. Hence, it is to be pointed out that the correlations of each of these tests against any validation criteria do not yield the same results, nor is it intended that they should, because each is selected to investigate a different aspect of personality functioning. It is true that each test supple-

ments the findings of the remaining tests of the battery with some overlapping but without duplication. This accounts for the increased sensitivity of a battery of tests in the detection of the presence of obscure, subtle or clinically evident organic brain pathology as compared to the sensitivity of series of tests or single tests. It would be irrelevant to this paper to discuss in detail the psychologic test protocols. Discussion of this will be presented in a future publication focusing on the psychologic protocols of the cases of the present study.

METHODS AND PROCEDURE

The charts of 16 adults between the ages of 17 and 60, suspected through the processes of history taking, neurologic examination or psychologic testing of having organic brain disease, were studied. All case records reviewed and selected met the following criteria: 1) there was a history suggestive of organic brain pathology; 2) a complete neurologic examination had been performed; 3) the psychologic test battery, as described above, had been administered; 4) electroencephalography was carried out in all but one case. Histories were first taken by the physician doing the routine intake examination and interview. In some cases a history suggesting organic brain pathology was noted by the psychiatric social worker in more detailed history taking. This was frequently repeated by the physician doing the psychiatric examination. Finally, the history was repeated in regard to brain injury, infection, etc. by the examining neurologist.

The neurologic examination was complete except for spinal fluid and electrical studies.[14] Because of the difficulties encountered in carrying out spinal fluid studies on private patients where there was no clinical indication, this procedure was not carried out; furthermore it was felt that its value as a correlating procedure was sharply limited, especially in the chronic cases.

The electroencephalograms were performed in an accepted electroencephalography laboratory and an opinion was expressed by a physician trained in their administration and interpretation. All cases were referred for this examination with the statement, "Organic brain disease is suspected." The electroencephalography findings were included in the study not because the electroencephalogram is an accepted method of detecting the presence of organic brain pathology, since no such claims are made, but rather because it is a procedure carried out almost routinely by many practicing clinical neurologists. It is also to be noted that the electroencephalography has been compared to psychologic testing in cases with organic brain disease.[13] It is therefore included in the study as an additional orienting set of findings.

TABLE 1

Case	History	Neurologic Examination	Electroencephalogram	Psychologic Test Battery: Memory	Thinking Processes	Perception	Affect	Speech	Motor Activity
1. Female, age 31	Blue incubator baby, prematurity? psychomotor epilepsy?	*Negative*	*Negative*	++	++	+	+	0	0
2. Female, age 26	"Brain fever," congenital internal strabismus	Staring facies, diminished automatic associated movements	"Tracing grossly abnormal, suggestive of diffuse pathologic or physiologic upset." *Positive*	+	++	+	++	0	+
3. Male, age 31	Severe head injury, age 3; severe toxemia, age 23	Tremor of extended fingers, intention tremor, hyperreflexia, nystagmus	*Negative*	++	++	+	+	0	++
4. Female, age 29	Ungovernable outbursts of rage—psychomotor epilepsy?	*Negative*	"Tracing shows poor organization with tendency to break down on hyperventilation; there is a tendency to paroxysmal dysrhythmia having characteristics of wave and spike defects seen in convulsive disorders." *Positive*	++	++	+	+	0	0
5. Female, age 40	Severe chronic alcoholism	Dysmetria, dysdiadokokinesis, tremor of fingers, dysarthria	*Negative*	++	++	++	++	0	++
6. Male, age 22	Longstanding schizophrenia—interim polioencephalitis sup.	Marginal Romberg, slight incoordination in hands	"Tracing shows moderate generalized abnormality of non-specific type." *Positive*	++	++	+	+	0	0
7. Female, age 41	Encephalopathy secondary to hyperinsulinism	Romberg, incoordination in walking, dysarthria, Hoffmann's sign, dysdiadokokinesis	"Tracing is of a type seen in variety of neuropsychiatric conditions—most frequently in affective states." *Plus-Minus*	++	++	+	+	0	++
8. Male, age 49	Severe head injury, craniotomy with psychosis	*Negative*	"Tracing shows rapid activity from all areas—felt due to generalized dissociation. Tracing considered to be borderline abnormal." *Plus-Minus*	++	++	++	++	++	++

TABLE 1—*(Continued)*

TABLE 1—*(Continued)*

Case	*History*	*Neurologic Examination*	*Electroencephalogram*	*Psychologic Test Battery*					
				Memory	*Thinking Processes*	*Perception*	*Affect*	*Speech*	*Motor Activity*
9. Male, age 47	Severe head injury	Left nerve deafness, dysdiadokokinesis, disturbed position sense, reduced touch and pain sensibility, left side	"Tracing considered very slightly abnormal on fast activity side." *Plus-Minus*	++	++	++	+	0	+
10. Male, age 21	Head injury, age 6 months?	Bilateral Chaddock's and equivocal Babinski signs	"Tracing considered generally abnormal with non-specific type of abnormality." *Positive*	++	+	0	+	0	++
11. Male, age 16	Clumsiness and retardation in school	Bilateral Chaddock's and Babinski signs	None performed—refused.	0	0	0	0	0	0
12. Male, age 37	Head injuries	Left nerve deafness, coarse tremor of hands	"Large amount of low voltage rapid activity present in large percentage of normals, also in large variety of N-P conditions—most frequently affective states." *Plus-Minus*	++	++	++	+	0	0
13. Male, age 40	Head injury	*Negative*	"Some suggestion of generalized abnormality arising on hyperventilation from symmetrical frontal derivation." *Plus-Minus*	++	++	++	++	0	++
14. Male, age 37	Electrocution through head to hand	Gait incoordination, dysdiadokokinesis, heel-to-knee dysmetria, pseudoathetosis, right hand, idiomotor apraxia, hemihypesthesia and hemiparesis	*Negative*	++	++	++	++	++	++
15. Male, age 43	Severe head injury	Romberg, bilateral Chaddock's signs, Babinski signs, hyperreflexia	"Tracing considered within limits of normal variation but some evidence of abnormal physiologic activity from frontal area—? evidence deep-seated general abnormality without focal significance." *Plus-Minus*	++	++	++	+	0	0
16. Male, age 60	Advancing age—depression	*Negative*	*Negative*	++	++	++	++	++	0

The battery of psychologic tests had been administered in every case before the study was planned, and in every case had been requested to aid the staff in arriving at a conclusion about the nature and treatment of the patient's total problem. It should be pointed out that all of the studied patients were referred to the clinic because of psychiatric problems.

CONTROLS

Inasmuch as the chief purpose of this study is an evaluation of the diagnostic sensitivity of the battery of psychologic tests for the detection of organic brain disease, controls on the entire clinical study were not carried out. Control was limited to an attempt to demonstrate that the battery of psychologic tests did not show evidence of the presence of organic brain disease when administered to groups of adults in whom there was no history suggestive of organic brain disease, all of whom carried a diagnosis commonly accepted as being entirely dissociated from organic brain disease. For controls the records of two groups of 16 patients each, all between the ages of 20 and 45, were selected consecutively. The first group carried a final diagnosis of schizophrenia, and the second group, a final diagnosis of some form of neurotic maladjustment. In all of these cases the same battery of psychologic tests had been administered.

SCORING

Attempts to score results in a study of this kind meet with almost unsurmountable difficulties. The essential facts of the histories suggestive of organic brain disease were simply recorded rather than scored as positive or negative. The findings on neurologic examination which indicated the presence of organic nervous system disease were listed in terms common to clinical neurologists. When as the result of the neurologic examination no alterations in neurologic physiology appeared, this examination was labeled negative for evidence of organic brain disease. It is recognized that neurologists differ somewhat in their interpretation of objective evidence of nervous system disease; for this reason the objective abnormalities are enumerated. No subjective symptomatology is included here.

Any attempt to score electroencephalographic findings for purposes of this study meet justifiable criticism. For this reason the concluding diagnostic paragraph of the encephalographer's report has been quoted in full whenever any question of abnormality is expressed. If the report stated that the tracing was within the limits of normal variation, the concluding paragraph was omitted and the term "negative" is used. Examination of the remaining results reveal many which might be regarded as "borderline" or "slightly abnormal" or "suggestive." Arbitrarily all of these have

been scored "plus—minus" inasmuch as they reflect inability on the encephalographer's part to state definitely the presence or absence of abnormality. The remainder of the encephalographer's reports are also quoted and scored "positive."

Finally an attempt to score the results of the battery of psychologic tests encountered difficulties. As noted above, evidence of "organic" brain disease in the use of psychologic tests appears in the area of memory, thinking processes, perception, affect, speech and motor activity. Psychologic test data for purposes of this preliminary study are recorded as to which of these areas of brain function are affected. These are simply listed in table 1. When the organic signs were more heavily stacked in one area, this was scored as 2 plus. If there were fewer signs in an area, it was scored as 1 plus, and if no signs appeared in an area in the protocol, it was scored as 0.

RESULTS OF CONTROLS

Sixteen cases with a final diagnosis of schizophrenia in whom there was no history suggestive of organic brain disease and to whom the same psychologic test battery had been administered before this study was contemplated, showed no evidence of organic findings in the psychologic test protocols. Sixteen cases with a final diagnosis of some type of neurotic maladjustment, also meeting the same criteria, showed uniformly negative results on administration of the test battery.

CASES OF UNUSUAL INTEREST

Attention is called to case number 6 which is of especial interest because an original complete examination had been carried out two years prior to the history of an attack of polioencephalitis in the summer of 1950. At the time of the first examination, psychiatric examination and the battery of psychologic tests both pointed to the presence of a long-standing schizophrenic process, and all procedures were negative for the presence of organic brain disease as well. Recently the diagnostic test battery was administered for the purpose of checking interim progress in psychotherapy. In addition to revealing the evidence of the schizophrenic process, the test battery revealed additional findings indicating the presence of organic brain disease. The patient's history was then rechecked and it was discovered that while in the South on a two months' vacation from psychotherapy he had suffered a moderately severe attack of polioencephalitis confirmed by laboratory and clinical fiindings. Neurologic examination at this time was little more than suggestive of organic brain disease, although the psychologic test battery revealed many organic

signs in memory, thinking processes, perception and effect, the signs being most prominent in memory and thinking.

Of special interest also is case number 7. This patient gave a typical history of chronic paranoid schizophrenia and sometime before she was brought to the clinic for examination had developed an untoward complication from what had apparently been an overdose of insulin. While details of this therapeutic accident are not complete, it is to be noted that neurologic examination revealed ample evidence of the presence of diffuse organic brain disease. In this case the test battery revealed the old schizophrenia process as well as the superimposed organic brain damage.

A third case is mentioned because it is the only case in which the test battery failed to reveal clearly the evidence of organic brain disease. This was case number 11, a 17 year old boy who had had a very marginal incoordination with some intellectual retardation with rather slow progress in school. The only findings on neurologic examination were bilateral Chaddock's and Babinski signs. The incoordination could not be detected on examination, but his history was suggestive of some clumsiness, especially earlier in life. From a clinical neurologic standpoint when one considers his history and examinational findings, this patient seemed to fall into the diagnostic entity of cerebral palsy and to be one of those cases in which the only objective neurologic evidence is the pathologic foot reflexes.

RESULTS AND SUMMARY

It is obviously difficult to draw any hard and fast conclusions from the findings (table 1). First of all, in order to draw any comparisons between one type of diagnostic procedure and another, one must assume that the condition he is trying to detect is actually present. Clinical opinions are subject to much variation, but it is believed, on the history of possible brain damage, infection, and the neurologic examinations, that all of the cases have some degree of brain damage or defect.

Assuming that all 16 cases have some organic brain pathology:

1. Routine neurologic examination detected organic brain disease in 11 of 16 cases or 68.8 per cent.
2. Fifteen electroencephalograms were obtained and of these, five were categorically reported as normal, thus the electroencephalogram revealed abnormal function in 10 of 15 cases or 66.7 per cent.

   If the "borderline" or rather indefinite reports scored as "plus-minus" are included among those which failed to diagnose abnormal brain functioning, the electroencephalogram revealed abnormal function in 4 of 15 cases or 26.6 per cent.

   An average of these two extreme percentages (46.6 per cent) would

compare favorably with the findings of Greenblatt, Levin and Atwell[13] who found the electroencephalogram abnormal in 44 per cent of organic cases. Choosing either method of scoring the electroencephalogram findings, if the neurologic examination and the electroencephalogram were used in combination for the detection of organic brain functioning, the percentage of accuracy would have been somewhere between 75 and 87.5 per cent.

3. The routine use of the psychologic test battery revealed evidence of organic brain disease in 15 of 16 cases or 93.7 per cent.

   If the neurologic examination and the psychologic test battery were used in combination in the sixteen cases, a diagnostic accuracy of 100 per cent would have been obtained.

CONCLUSIONS

The present findings would appear to indicate that an experienced clinical psychologist employing a selected battery of psychologic tests over a considerable period of time in the examination of a wide range of psychiatric and neurologic disorders in the late adolescent and adult age groups, is able to detect evidence of organic brain pathology with a degree of accuracy greater than that obtained by clinical neurologic examination or by electroencephalography used alone. Additional studies are indicated to evaluate further the sensitivity of psychologic test batteries as diagnostic aids in the detection of organic brain disease.

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Action of Adrenaline and Noradrenaline on the Tremor in Parkinson's Disease

Henry Barcroft, M.D., Elizabeth Peterson, B.A.
and Robert S. Schwab, M.D.

THE tremor of a patient with Parkinson's disease increases with emotional tension.[1] The mechanism of this effect is not clear but is probably related to an increase in tone or tension of the voluntary skeletal muscles. The classical experiments of Cannon[2] have shown that in animals an adrenaline-like substance is liberated during emotional stress, and this has been confirmed in man by Doupe.[3] The purpose of this paper is to describe the effects of intravenous administration of both adrenaline and noradrenaline (Arterenol) on the tremor of Parkinson's disease.

Modifications of these findings by the antispasmodic drugs useful in the treatment of Parkinson's disease will also be described.

METHODS AND CLINICAL MATERIAL

The action of adrenaline and of noradrenaline on the blood pressure and heart rate in a group of normal men has been reported previously.[4-7] The technique of these investigators was followed here with certain modifications and was as follows:

All patients were examined in a comfortable chair. Surface electrodes were placed on both extensor and flexor muscles of one forearm. The output of these was led to a Grass ink-writing electroencephalograph. A voltage integrator[8] was attached to the electromyogram that was most active. The integrated voltage output of this apparatus was indicated on the oscillograph paper by the pen of one of the channels in the form of short pen marks. These were calibrated in millivolts per mark per minute. Another channel was used to record the electrocardiogram for the continuous measurement of heart rate. Identical settings of all of these were arranged for each patient who was studied under different drug situations.

From the department of physiology, St. Thomas's Hospital, London, England, and the Brain Wave Laboratory, Massachusetts General Hospital, Boston, Mass.
This work was supported by a grant from the Office of Naval Research, Project VIII.

A sphygmomanometer cuff was fitted around the same arm above the elbow for taking the arterial blood pressure by the auscultatory method at intervals of one minute. The skin over a vein in the other arm was anesthetized with 2 per cent Procaine to eliminate any needle pain.

The time procedure was as follows: A baseline of electromyogram, electrocardiogram and arterial blood pressure was recorded for 5 minutes. Then the needle was introduced into the vein and normal saline administered at a rate of about 2 ml. per minute for approximately 5 minutes. The syringe was then changed and adrenaline or noradrenaline infused at a rate of 10 micrograms per minute (in 4 ml. saline per minute). The adrenaline infusion was usually intended to last 5 minutes but often terminated earlier due to excessive tremor or too great elevation of the blood pressure. As soon as this infusion was over the needle was removed from the vein. Recording continued for another 10 minutes.

Three types of experiments were done:

1. The action of adrenaline was investigated in patients after withdrawal of medication.
2. The action of noradrenaline was investigated in patients after withdrawal of medication.
3. The action of adrenaline was investigated in patients on medication.

All patients had a definite parkinsonian syndrome with the usual tremor and were ambulatory. No attempt at etiological classification of the cases was made.

The drugs used for medication were Benadryl,[9] Parpanit[10] and Artane.[11] Individual patients were being treated with one or more of them as experience showed which suited them best. In the experiments done off medication no drugs had been taken since the evening before.

RESULTS

Action of adrenaline after withdrawal of medication.

The results of 14 experiments, each on a different subject, show that there was definite visible increase in parkinsonian movements in nine patients during the adrenaline infusion. This was quite apparent to both observer and patient and was often so marked that the infusion was stopped prematurely to avoid distress.

The electromyogram results provide objective evidence of the same effect. During the initial resting period the average rate of integrator signals was 12 per minute. During the administration of saline the rate rose by 5 signals per minute, probably owing to the psychic effect of the procedure. During the administration of the adrenaline-saline mixture

the rate rose very markedly by 28 signals per minute. This was more than three times the rate during the resting periods, and presumably was due to the adrenaline. After removal of the needle in the final resting period the integrator rate returned almost to its initial level.

Changes in the integrator signal rates during the infusions of adrenaline are shown graphically in figure 1. It will be seen that the rate was increased in every experiment. The figure shows that while there was good agreement between results of the electromyogram and those of clinical inspection in many cases, this was not so in others. This may have been because each method of assessment is different. The eye judges the amplitude of the rhythmic movements. The electromyograph records the much more complex algebraic sum of action currents generated by both rhythmic movement and static rigidity (figure 2). Changes in rigidity are not taken into account by the eye.

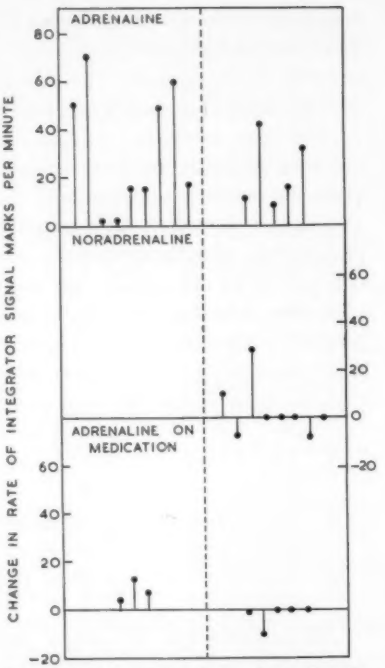

FIG. 1. Effects of adrenaline and noradrenaline on electromyogram. Those obtained in experiments in which there was clinical increase in the tremor are to the left of the vertical dotted line; those obtained in experiments in which there was no clinical increase in the tremor are to the right.

Adrenaline increased the average systolic pressure by 16 per cent and the diastolic by 8 per cent and caused an increase in heart rate of 18 per cent. These findings are similar to those found by Barcroft and Konzett[7] in normal subjects.

Action of noradrenaline after withdrawal of medication.

The results of eight experiments on seven subjects demonstrate that in no case was there any significant increase in parkinsonian movements. This is in accordance with the electromyogram results and integrator signals. The integrator signals remained almost constant during the four periods of rest, saline, noradrenaline and rest. The effect of noradrenaline on the integrator signals is also shown in figure 1.

Noradrenaline increased the average systolic blood pressure by 23 per cent, the diastolic by 20 per cent, and reduced the heart rate by 8 per

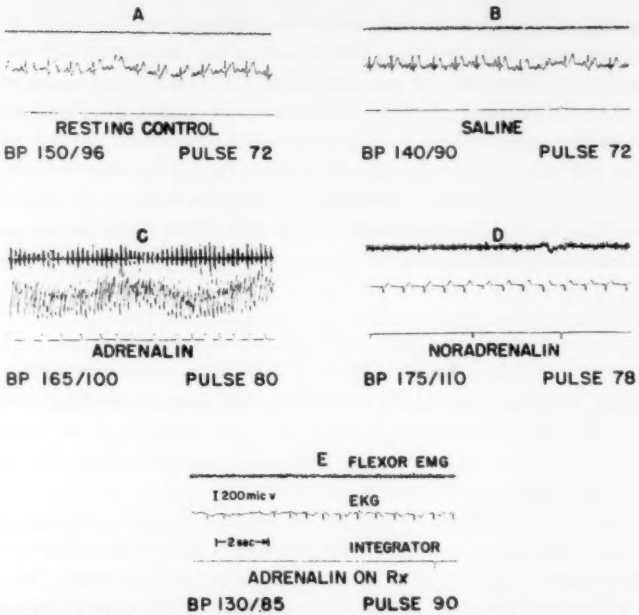

FIG. 2. Examples of the electromyogram from the right flexor digitorum communis (surface electrodes), during (A) resting period (control); (B) saline injection; (C) adrenaline injections; and (D) noradrenaline injections—off all drugs and (E) adrenaline injection on drug (Panparnit, 6 tables, 50 mg. each, orally during day—regular medication of this patient, P. L.).

Calibrations same in all 5 (shown in E). Blood pressure as marked. EKG, line II (completely obscured by tremor in (C). Line III, integrator clicks.

cent. These changes are comparable to those found in normal subjects.[7]

Figure 1 shows the contrast between the action of noradrenaline on the parkinsonian tremors and that of adrenaline. In no patient did noradrenaline have any significant visible effect on the tremors though adrenaline increased them in more than half the patients. It had scarcely any effect on the movements as judged by the integrator signals, whereas adrenaline increased them, on the average, threefold.

Action of adrenaline in patients on medication.

The results of eight experiments on seven subjects show that adrenaline caused clinical increase in the tremor in only three cases. This was confirmed by the electromyogram; it will be seen that the rate of the signals was practically unaffected by adrenaline. This is also seen in figure 1.

The changes in blood pressure and pulse rate show little variation from the normal.

Figure 1 shows that during medication adrenaline had far less effect on the parkinsonian tremors. While adrenaline increased the tremors visibly in more than half the patients off medication, it had no significant effect in any of the patients on medication. Off medication, according to the integrator signals, adrenaline increased movements on the average threefold but it had scarcely any effect when on medication.

This may well open up a quantitative approach to rapid assay of the possible benefits of drugs in this condition and throw light on the site and mechanism of the action of these drugs.

DISCUSSION

An explanation of the enhancing effect of adrenaline on parkinson movements would be of great interest. It will be remembered that the adrenaline infusions caused hypertension, but the possibility that this was in some way responsible for increasing the tremors can be ruled out on the grounds that noradrenaline infusions did not affect the tremor though they caused even greater hypertension.

Infusions of adrenaline sometimes caused subjective symptoms, most commonly palpitations and slightly increased breathing. These might have caused some apprehension and might have increased the tremor. It has been shown that the parkinsonian tremor is increased by mental effort under minimal stress of hurry and concentration. The subject tested as in the previously reported experiments is told during recording of blood pressure to subtract 7 from 100 as fast and accurately as possible. An examiner stands by him, stop-watch in hand, writing down each answer as it is given. Any slowness or delay brings out the words, "Hurry", "Come on", "Yes?" In all cases (15) the tremor increased, and the blood pressure rose 10 to 20 points both returning to normal promptly at the end of the test. This probably involves autonomic stimulation but whether adrenaline or noradrenaline rises in the blood is not known.

Furthermore we have shown[12] that apomorphine (a parasympathetic stimulant) slows the pulse, depresses the blood pressure and reduces the tremor in Parkinson's disease. The reduction of blood pressure by amyl nitrate or near syncope does not affect the tremor.

There is considerable evidence in neuropathologic studies that the midbrain reticular substance is involved in Parkinson's disease. This area when stimulated increases skeletal muscle tension. Not only is it close to the autonomic centers in the hypothalamus but there is some evidence of connections. Therefore, it may be that in Parkinson's disease the effects of adrenaline and apomorphine on the tremor are related to their influence on the cells in this area of the mesencephalon.

This explanation would fit in with the fact that noradrenaline had no effect on the tremor, since subjects are usually quite unaware of any change from the saline when noradrenaline is being infused. However, apprehension is probably not the explanation since in some subjects the increase in the tremor seemed out of all proportion to the trifling symptoms experienced.

Granting then that adrenaline probably acts on the neuromuscular system at some level lower than consciousness, is its action peripheral or central? This could be settled definitely by investigating its effect on the movements during intra-arterial infusions into the limbs. This was not possible during the time available and will form the subject of a further study. However, the action is probably central, for some normal subjects exhibit tremor when adrenaline is given intravenously. This does not appear to happen when the adrenaline is given peripherally directly into the artery.[4, 13, 14] The fact that the tremor in normal subjects is probably due to a central action of adrenaline suggests that adrenaline may act centrally on parkinsonian tremor. A central action of adrenaline in man has also recently been described by Swan.[15]

The reason why adrenaline stimulates the parkinsonian movements while noradrenaline does not is unknown. It is probably of fundamental significance to the physiology of the nervous system. There are other instances of differences in the action of the two sympathomimetics for example:

	Adrenaline	*Noradrenaline*	*Authors*
Heart rate	Tachycardia	Bradycardia	Goldenberg et al.[5]
Muscle blood flow	Transitory initial dilatation	Absent	Barcroft and Konzett[7]
Accelerating action in carbohydrate metabolism	Marked	Little	Sutherland[16]

The question arises as to how far the increase in the tremor of parkinsonian patients during emotional stress is due to adrenaline secretion by the suprarenal glands. Recent work suggests that adrenal secretion may be largely noradrenaline which would not affect the tremors. It seems impossible to settle this question until reliable methods are available for measuring the amounts of adrenaline and of noradrenaline in the blood.

It will be remembered that when the patients were on medication the adrenaline had much less effect on the tremors. The mechanism of this is not very clear. Of the medicines used Benadryl (Loew)[17] alone had an

adrenolytic action in the usual pharmacological sense. Parpanit[18] and Artane[19] have not been credited with any adrenolytic action. However, since adrenaline increases the parkinsonian tremor, it would be of interest to see if the tremor can be decreased by adrenergic blocking agents.

SUMMARY

1. The effect of intravenous adrenaline and noradrenaline on the tremor of Parkinson's disease has been investigated in 15 patients.
2. In more than half the patients adrenaline caused a marked increase in the tremor.
3. In no patient did noradrenaline have any significant effect.
4. The effect of adrenaline on the tremor was much reduced when the patients were being treated with the so-called antispasmodic drugs.
5. The effect of adrenaline on the tremor was not due to the rise in arterial blood pressure, nor is it due solely to apprehension. Some other action is involved, probably in the central nervous system.
6. The reason why adrenaline enhances the tremors while noradrenaline does not is unknown. Examples are cited of other instances in which the two substances have different actions.
7. The reason why the antispasmodic drugs used in the treatment of the disease reduce the effect of adrenaline on the tremors is unknown.

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Neurology

Clinical Pathological Conference

From the Department of Neurology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute, Presbyterian Hospital, New York

Presented by
H. Houston Merritt, M.D. and Abner Wolf, M.D.

PRESENTATION OF CASE

A 46 year old white female was admitted on April 30, 1951, with complaints of fever for six weeks, paraplegia progressing to quadriplegia for two and one-half weeks, and progressive deafness and tinnitus of two weeks' duration.

History: This was the first admission to the Neurological Institute of a housewife, who was apparently well until five and one-half years ago, when while driving a car, she experienced what was described as a "peculiar sensation" as if she were "far away." She was able to drive her car into the garage and proceed into the house at which time she commenced to prespire and still had the peculiar sensation. The peculiar feelings became localized to her left upper and lower extremities, and these felt as if they did not belong to her. The feelings cleared within a period of one week, but two weeks later they recurred together with a feeling as if she were going to faint. She again prespired profusely and had mild photophobia, associated with peculiar visual sensations resembling hallucinations. An electrocardiogram at this time was negative as were several other investigative tests, and she was treated for nerves and the menopause. Another bout occurred four to five months later in 1946.

The patient was in good health and had no complaints from 1946 to March 17, 1951, about six weeks prior to admission, when she experienced malaise, weakness, anorexia and a fever of 102°. The temperature did not respond to treatment with penicillin and in fact rose to 105° on March 17 at which time she was admitted to a nearby hospital. Other than general malaise, there were no specific complaints and her temperature returned to normal after a few days. About April 10 while still hospitalized, the fever recurred and the patient was told that she had a virus infection of the lungs. She was treated unsuccessfully with penicillin, Terramycin and Chloromycetin. At approximately this time she noted the onset of diplopia and difficulty in her vision and complained of pain in the shoulders and arms. Report from the opthalmologist who examined the patient at this time stated that the difficulty in vision was due in part to a scotoma in the temporal field of the right eye. Within a few days it was noted that the patient was unable to move her lower extremities. This weakness gradually

spread to involve the upper extremities, and by April 13 there was a complete quadriplegia with impairment of sensation of pain in the lower extremities. Difficulty in voiding developed and patient was placed on catheter drainage of the bladder. The pain in the shoulder region became more severe and her neck became stiff. About the same time the patient began to develop tinnitus in both ears and rapidly became totally deaf. Four days prior to admission her face became swollen without known cause, and at the time of admission, she was having respiratory difficulty.

Examination of the cerebrospinal fluid on April 11, 1951 showed 57 white cells, all lymphocytes, and a protein content of 320 mgms. On repeat examination at time of myelogram on April 24 there were 383 white cells, all lymphocytes, and a protein content of 1,000 mgms. The myelogram was reported as showing partial obstruction at the lumbodorsal junction, and a widening of the canal at the cervicodorsal junction.

Physical Examination: At the time of admission the patient was completely deaf and did not respond to verbal commands but was able to cooperate when the commands were written. Voice was weak but speech otherwise appeared to be fairly normal. She was oriented as to time, place and person but most of the facts with regard to her illness were obtained from the record of the other hospital and her relatives. The temperature was 98.6°, pulse 120, respirations 28 and blood pressure 160/80. There was severe nuchal rigidity and limitation of motion of the hand in all directions. Examination of the heart was normal. Numerous rhonchi were heard throughout the lungs, but there was no evidence of any focal consolidation of the lungs.

Neurologic Examination: Pupils were small and reacted sluggishly to light. On examination of the fundi, there was slight pallor of the optic discs particularly on the temporal side. Accurate tests of the visual acuity and fields could not be made. There was a slight weakness of the right side of the face, greater in the muscles of the lower half. There was impairment of lateral gaze in both directions and there was weakness of the left internal rectus muscle. There was total deafness to the spoken voice and watch. Bone conduction and air conduction was lost in both ears when tested with the tuning fork. There was a flaccid paralysis of all of the muscles of the trunk and extremities and respirations were labored. Sensory examination was difficult because of the patient's deafness. Pin prick and brush were felt everywhere but there was a quantitative diminution of these sensations below the level of approximately the fourth thoracic segment. The tendon reflexes were absent in the arms and legs. The plantar responses were absent and no abdominal reflexes were obtained. The jaw jerk was 2+. The patient was incontinent of urine and feces.

Laboratory Examination: Blood: Hgb. 13.7 gms., RBC 4.05 M., WBC 10,000, 89 per cent polys. Mazzini negatives. ESR 20 mm/1 hr. Serum protein 6.5 gm. Albumin 4.1 gm. Globulin 2.4 gr. Urine: Sp. Gr. 1.018, albumin 2+. Acetone 2+ Glucose negative. Many white cells in the sediment. Urine culture: B. proteus, B. aerogenes, CO_2 55 volumes per cent. Chlorides: 489 mg. per cent. Lumbar puncture: Initial pressure 190 mm., manometrics were open, fluid contained large amounts of pantopaque and showed 600 Wbc, 100 per cent lymphocytes, total protein 456 mg. per cent, sugar 68 mg. per cent, chloride 705 mg. per cent. No organisms were found on smear or culture. X-rays: Cervical and thoracic spine normal. Skull: Slight demineralization of the dorsum sellae, suggesting increased intracranial pressure. The pineal was 1 cm. posterior to the normal zone. Gas myelogram: Visualization of the spinal canal was not satisfactory. However, a small amount of gas was present in the left lateral ventricle which was not enlarged or displaced. Pantopaque myelogram: Radiopaque material flowed slowly throughout the entire length of the vertebral canal. Oil passed into the cranial cavity. In the cervical region, there appeared to be widening of the cervical cord from C3 to C6 suggesting an expansive lesion of the spinal cord.

Course in Hospital: The patient was

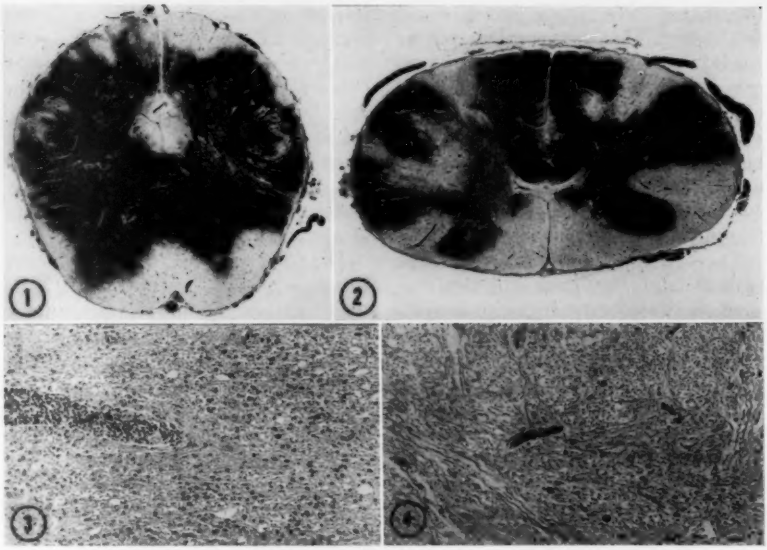


FIG. 1. Lower medulla. Many areas of demyelination. Mahon stain, X6.

FIG. 2. Sixth cervical segment of spinal cord. Multiple zones of demyelination. Mahon stain, X6.

FIG. 3. Sixth cervical segment of spinal cord. Lateral column. Foci of increased cellularity are areas of microglial proliferation and phagocyte formation. Perivascular infiltration by lymphocytes. Hematoxylineosin stain, X65.

FIG. 4. Sixth cervical segment of spinal cord. Relative preservation of axones in demyelinated area. Romanes stain, X65.

placed on constant tidal drainage for the bladder and antibiotics were given to combat the urinary infection. There was no change in her general condition until about the third day after admission when the temperature rose to 103° and the respirations became rapid and labored. The patient was placed in a respirator and given oxygen by nasal tube. She was unable to synchronize her respirations with the movements of the respirator. Sedation and electrophrenic stimulation was given at varying intervals. On the fourth day the temperature rose to 105° but fell to normal on the sixth day, that is the day before death. On the day of death, respirations became more difficult because of an excess accumulation of secretions in the larynx and its was felt that a tracheotomy would be required. During intubation the patient became cyanotic and immediate tracheotomy was performed. Tracheotomy tube was connected with oxygen and artificial respiration was given for 25 minutes without response.

CLINICAL DISCUSSION

DR. MERRITT: The clinical course of this patient was of short duration, lasting approximately two months. The onset appeared to be that of an acute infectious disease with elevation of body temperature. The fever persisted for several weeks but the neurological symptoms did not begin to make their appearance until approximately two weeks after the onset of the febrile episode. The first neurologic symptoms was difficulty in vision in

the nature of diplopia and a visual field defect. This was soon followed by pains in the upper extremities and progressive weakness of all of the muscles of the trunk and extremities so that approximately three and a half weeks before her death there was complete paralysis of all extremities, incontinence of urine, weakness of the respiratory muscles and deafness.

The severity of the illness of the patient and the complete deafness made it difficult to perform an entirely satisfactory examination, particularly with regard to the sensory modalities. From the information obtained through writing it appears that the patient's mental faculties were not severely impaired. From the admittedly inadeqate neurologic examination, it was apparent that the patient had many lesions within the nervous system. From the symptoms and signs we can state that there was involvement of the mid-brain to explain the difficulty in the eye movements; involvement of the brain stem to explain the deafness and nystagmus. Diffuse lesions in the spinal cord must be postulated because of the extent of paralysis and the absence of the reflexes.

In the diagnosis of this patient's illness, the following possibilities should be considered: 1. Acute infection with filtrable virus. 2. Acute polyneuritis. 3. An acute demyelinizing process. 4. Diffuse spread of malignant neoplasm.

An acute infection with a filtrable virus of the equine or St. Louis type can produce multiple lesions within the central nervous system and the cerebrospinal fluid findings are not incompatible with this diagnosis. Extensive cord involvement in virus diseases is rare, and it does not seem likely that this patient had an acute virus disease.

Acute polyneuritis of the so-called Guillain-Barre type must be considered in the differential diagnosis because of the widespread flaccid paralysis and the loss of the tendon reflexes. Against this diagnosis is the onset with diplopia and visual field defect. It is known that any of the cranial nerves may be involved for polyneuritis to affect the optic, oculomotor, and auditory nerves without also involving the facial nerves.

The diagnosis of malignant neoplasm is possibe but warrants little consideration. Diffuse carcinomatosis of the meninges with nodules in the brain and spinal cord could explain the clinical picture as could also dissemination of a meduloblastoma of the cerebellum. The evolution of the symptoms is hardly compatible with either of these diagnoses.

The diagnosis which would seem to best explain all of the patient's signs and symptoms is an acute demylinizing process such as acute multiple sclerosis or an acute encephalomyelitis. Plaques in the mid-brain and in the brain stem would explain all of the cranial nerve symptoms and diffuse lesions in the spinal cord would explain the paralysis and loss of reflexes. It is uncommon for patients with multiple sclerosis to have a cell count in the spinal fluid greater than 100 cells or a spinal fluid protein greater than 100 mgms. but this is not true of the acute fulminating cases. This diagnosis would also explain the transient symptoms which occurred five and a half years before the patient's acute terminal illness.

I believe the autopsy will show widespread areas of acute demyelinization throughout the brain stem and spinal cord. Perhaps an incomplete transverse lesion in the upper cervical region with edema and swelling of the cord will also be found to explain the myelographic findings. There may also

be old sclerotic lesions as a residual of the earlier episodes.

CLINICAL DIAGNOSIS: *Acute multiple sclerosis.*

PATHOLOGICAL DISCUSSION

DR. WOLF: The lesions found upon postmortem examination were fairly large foci of complete demyelination in the spinal cord, medulla, and pons. They were more frequent in the superficial portions of the white matter but also extended into the deeper areas and often into the grey matter, as well, in wedge-shaped fashion. The process was more extensive in the sacral and lumbar segments of the spinal cord where there was a diffuse total, or almost total loss of myelin sheaths due to the confluence of multiple, large lesions. The lesions at higher levels of the neuraxis were for the most part discrete, marginal and unsystematized. A few were found in the midbrain, thalamus, internal capsule, fornices and optic chiasms, but none in the white matter of the cerebral hemispheres or cerebellum. All the lesions were of approximately the same age and were marked by relatively good preservation of the axis cylinders, a pronounced microglial reaction with diffuse and perivascular accumulation of large mononuclear phagocytes and only a mild astrocytosis. The diffuse margin of some of the lesions and the presence of small myelin sheaths toward their edges, suggested that degeneration was still in progress at death. There was a moderate perivascular lymphocytic infiltration in and about the lesions, and some lymphocytes and occasional plasma cells in the leptomeninges and subarachnoid space.

Taken as a whole, the changes were essentially those of so-called acute multiple sclerosis. The lesions were in a comparatively early stage of evolution and were concentrated in the lower portions of the neuraxis, largely sparing the cerebral white matter and the ventricular walls. Their subacute character corresponded approximately to the clinical course of two months. No old plaques, such as might be correlated with the patient's "peculiar sensations" and other vague neurological complaints of five years before, were found, so that these symptoms can probably be regarded, in retrospect, as unrelated. The concentration of the process in the spinal cord and brain stem together with the occurrence of the lesions in the optic pathways raises the question as to whether this case does not belong in the rather vaguely defined group of optic neuromyelitis, which indeed may be no more than a variant of multiple sclerosis. The absence of necrotizing lesions in the spinal cord is against this. The onset of the patient's illness shortly after a febrile episode described as a virus infection and the presence of occasional focal perivascular demyelinating lesions, raises the question of whether this is an instance of disseminated encephalomyelitis. The nature of the majority of the lesions, however, is against this classification and the close affinity, if not identity, of acute multiple sclerosis with acute disseminated encephalomyelitis, might render such a distinction of little value. The cerebrospinal fluid block and myelographic findings may have been due to swelling of the spinal cord associated with acute lesions in the cervical region. The other symptoms are adequately explained by the involvement of the spinal cord and brain stem.

ANATOMICAL DIAGNOSES: *Acute multiple sclerosis.* Pneumonia, lobular, bilateral. Adhesions, fibrous pleural, bilateral. Arteriosclerosis, generalized, mild.

Case Report

Two Cases of Amyotrophic Lateral Sclerosis Treated with Cortisone

Sherwood A. Jacobson, M.D.

No specific treatment for amyotrophic lateral sclerosis has been developed as yet. However, cortisone has been effective in many of the diseases which are thought to result from perversion of the adaptation mechanism, and since amyotrophic lateral sclerosis has been on occasion included in this group, cortisone has been suggested in the treatment of this disease.

The following report deals with two typical cases of amyotrophic lateral sclerosis treated with what was considered to be an adequate course of cortisone. The dosage schedule was 200 mg. on the first day and then 100 mg. daily until a total of 3 Gm. was administered. Although this report presents only two cases, it is considered worthy of inclusion in the literature because of the careful documentation of the cases and the definiteness of the results.

A review of the literature revealed no definite conclusions as to the efficacy of this therapy. In the Proceedings of the First Clinical ACTH Conference,[1] two cases treated with ACTH were reported, only one of which was detailed. Both of these showed only slight response to the therapy, and the results were considered inconclusive. Bernard[2] had previously reported the treatment of three patients with adrenal cortical extract for two months without effect. Carlisle[3] mentioned briefly that data was incomplete and inconclusive as to the benefit of cortisone in the treatment of amyotrophic lateral sclerosis, but made no mention as to dosage or number of patients treated.

REPORT OF CASES

Case 1.—A 50 year old white male bartender was admitted to the Saratoga Veterans Administration Hospital on August 29, 1950 and transferred to the Bronx Veterans Administration Hospital on October 28, 1950. His chief complaint was weakness of the left arm and hand. The patient first noticed weakness in the fingers of the left hand six months before admission, with progression but no change in perception of sensation. About a month prior to admission his left leg also became weak, and he began to drag his left foot. There were no other complaints. In 1943

From the department of neurology, Veterans Administration Hospital, Bronx, New York.
Reviewed in the Veterans Administration and published with the approval of the chief medical director. The statements and the conclusions published by the author are the result of his own study and do not necessarily reflect the opinion of policy of the Veterans Administration.

the patient had suffered the fracture of several ribs and the eleventh and twelfth dorsal vertrabrae; there had also been trauma which was associated with unconsciousness for four days following the accident. The only residual of this was occasional dull localized headaches at the vertex. Family history was essentially negative.

Examination: On admission he had a blood pressure of 215/130 mm. Hg. There was moderate wasting of the muscles of the tongue. The left hand was held in a claw hand position. There was moderate diffuse wasting of the small muscles of the left hand and flexors and extensors of the left forearm and arm; moderate atrophy of the deltoid and infraspinatus muscle of the left shoulder; marked fasciculations of the muscles of the shoulders and all extremities; and weakness and decreased resistance to passive stretch in the left arm and leg. Deep reflexes of the left upper extremity were increased over those of the right, the superficial abdominal reflexes on the left were less than those on the right. Deep reflexes of the right lower extremity were less than those of the left lower extremity. There was a Babinski sign on the left. The jaw reflex was normal. On walking the patient dragged his left foot. With dynamometer testing he could squeeze to 38 kilograms on the right and 0 on the left. As to trunk strength, he was able to rise to only an angle of 30 degrees without assistant of his upper extremities. Strength in the right lower extremity was estimated to be about 50 per cent of normal and in the left lower extremity was estimated to be about 25 per cent of normal.

Lumbar puncture revealed a normal initial pressure and normal cerebrospinal fluid dynamics, with jugular compression with the head in the mid-position and in marked extension and marked flexion. The fluid was clear and colorless; there were no cells; the serology was negative and the protein was normal. Electroencephalogram showed no abnormality. A complete radiological survey of the cervical spine revealed a diffuse osteoporosis consistent with the age of the patient and no other abnormalities; x-ray plates of the skull were essentially negative. Complete blood count, urinalysis, blood serology, and blood chemistry studies were within normal limits.

Hospital course: The patient was started on a course of intramuscular cortisone, 200 mg. intramuscularly on the first day and 100 mg. daily thereafter until 3 Gm. were administered (29 days). Throughout the entire course a detailed daily record was kept of his condition. It was noted whether any fasciculations of the head, neck, arms, trunk or legs were present. Gait was observed, and testing of the grip by means of a dynamometer was recorded. Strength of trunk was checked by seeing whether the patient could rise from the bed without assistance of his arms, and the strength of the legs was also noted. The reflexes were carefully tested. Also recorded was his appetite, blood pressure and mental status. He was weighed daily. Blood potassium and sodium determinations were done weekly, fasting blood sugar determinations were done twice weekly, and urinalysis three times a week.

While under therapy the patient became much more cheerful. Blood pressure remained between 150 and 170 only on one occasion going up to 190. Midway through the course it was noted that the left Babinski response became more marked. Throughout the course of therapy it was noted he had a progressive decrease in tolerance to walking. His weight remained stationary, fasciculations in the lower extremities were only noticed on occasion, as were fasciculations in the left upper extremity. Atrophy appeared to remain as noted previously.

On the last day of therapy it was noted that he had no fasciculations of the head, neck, left upper extremity, trunk or lower extremities. There were slight fasciculations of the right upper extremity. His grip was 25 kilograms on the right and 0 on the left. He was only able to raise his trunk to about 30 degrees from the bed unassisted. Right lower extremity strength was estimated to be about 50 per cent and

left lower extremity strength was estimated to be 5 per cent of normal. Reflexes in the right upper extremity were hyperactive, in the left upper extremity decreased. The superficial abdominals were active on the right. The deep reflexes in lower extremities were hyperactive, the right being greater than the left. There was no clonus; there was a right Babinski response.

The patient was carefully followed after termination of the treatment, and two weeks after the end of therapy it was noted that there had been no change in his status except for marked fasciculations of both upper extremities. He was able to walk only 75 yards instead of 100 as previously noted. The abdominal reflexes were bilaterally absent and the deep tendon reflexes in the lower extremities were equally hyperactive. Examination one month after therapy shows further slight but perceptible progression of the disease.

Case 2:—In the second case noted, another patient with an almost identical clinical picture was treated and followed in the same fashion as Case 1. The patient showed no improvement during, at termination, and one week after the termination of the therapy. This case is not reported in detail as it merely complements the result noted in the first case.

SUMMARY

This is a report of two patients with clinical pictures typical of amyotrophic lateral sclerosis who underwent one month's therapy with 3 Gm. of cortisone, without any significant change except that which could be explained by the natural progression and variations of the disease process.

CONCLUSION

Intramuscular cortisone (3 Gm. in 29 days) had no effect on two patients with amyotrophic lateral sclerosis.

REFERENENCES

1. Proceedings of the First Clinical ACTH Conference, Philadelphia, Blakiston, 1950, p. 595.
2. Bernard, R. D.: Rectal administration of tolserol: The therapeutic effacy of this route as demonstrated in amyotrophic lateral sclerosis, N. Y. State J. Med. 49:2190, 1949.
3. Carlisle, J. M.: Cortisone (compound E): Summary of its clinical uses. Brit. M. J. 1:590, 1950.

The causes of the attack of congestion or haemorrhagy within the head, are predisposing and exciting: the former are plethora, repletion, or, on the contrary, exhaustion, inanition, or debility; disease of the heart, especially hypertrophy, and contracted valves, of the left side; some forms of acute anasarca; deranged or suppressed function of the kidney; disease of the arteries or veins, or other tissues within the cranium; &c. The exciting causes are excess in eating; muscular efforts, especially straining, vomiting, sneezing, passion; the recumbent posture, &c.

As inflammation usually assumes an *acute* character, congestion and haemorrhagy are, as generally, *sudden* in their attack.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

Neurology

Harold Robert Carter, M.D., 1907-1951

In the death of Harold R. Carter on October 28, 1951, the American Academy of Neurology has lost one of its most faithful members. He died as result of an automobile accident near Casper, Wyoming.

Born in Battle Creek, Michigan on April 11, 1907, Dr. Carter received his medical degree from the College of Medical Evangelists in 1932. Following internships in the Los Angeles County and the Santa Barbara General hospitals, he practiced medicine in San Ysidro, California from 1933 to 1935. After completing a postgraduate course in psychiatry and neurology in the Veterans Administration Facility at Palo Alto, California, he was a neuropsychiatrist with the Veterans Administration until 1937 when he was commissioned a first lieutenant in the medical department of the United States Army. In 1938 and 1939 he attended the Army Medical School, Washington, D. C. and the Medical Field Service School, Carlisle Barracks, Pennsylvania.

During a term of duty as neurologist in Walter Reed Hospital, Dr. Carter contracted undulant fever and later fell a victim to spondylitis of the Marie-Strümpell type. He subsequently served as a consultant in neurology and psychiatry while under treatment at the Army and Navy General Hospital, Hot Springs, Arkansas. Because his physical disability was considered too great for active service under wartime conditions, he was retired in 1942 with the rank of captain.

Dr. Carter's active professional life after he moved to Denver in 1943 would have been a credit to any physician. He became associated with the Neurological Institute of New York as a resident in 1944, devoting considerable time to the study of multiple sclerosis. He was assistant professor of neurology at the University of Colorado School of Medicine and during his later years in Denver studied intensively a number of cases of olivopontocerebellar atrophy in a Spanish-American family.

In the spring of 1951 Dr. Carter organized a local chapter for Recovery, Inc. Under his able guidance an unusually enthusiastic group of patients afflicted with psychosomatic disorders was soon assembled. At the time of his death he was in Wyoming primarily to help with the organization of a similar group. He attended meetings of the numerous professional organizations to which he belonged

with an unusual degree of regularity. In recognition of his services to the Cerebral Palsy Clinic of the Children's Hospital in Denver, a fund has been created in his name to aid in the work of that clinic.

Despite his painful affliction and the demands of a large private practice, Harold Carter, to the amazement of his friends, skated with his wife and two children, supervised the raising of steers by his son, and marched with the Shrine band in which he played an instrument. He loved music of both the popular and symphonic varieties. In his quiet and unpretentious way, Harold seemed to enjoy life to the fullest extent.

LUMAN E. DANIELS

PROGRAM OF THE
AMERICAN ACADEMY OF NEUROLOGY
Second Interim Meeting
April 24 and 25, 1952
BROWN HOTEL LOUISVILLE, KENTUCKY

REVIEW COURSES IN NEUROROENTGENOLOGY, NEUROPATHOLOGY, ELECTROENCEPHALOGRAPHY

Intensive review courses in neuroroentgenology, neuropathology and electroencephalography will be given preceding the meeting, sponsored and arranged by the American Academy of Neurology. Courses will be held as follows:

Neuroroentgenology—April 22, 1952
Neuropathology—April 22 and 23, 1952
Electroencephalography—April 23, 1952

Registration for the meeting starts at noon on Wednesday, April 23. All non-members are invited to attend the meetings and participate in the review courses.

THURSDAY, APRIL 24, 1952

Morning Session 9:00 a.m.
Chairman: Russell T. Costello, M.D., Detroit, Michigan
Secretary: Howard W. Gillen, M.D., New Orleans, Louisiana

Effect of 3-Hydroxyphenyl dimethylethylammonium Chloride (Tensilon) in Myasthenia Gravis
MARTHA R. WESTERBERG, M.D., KENNETH R. MAGEE, M.D. and FREDERICK E. SHIDEMAN, PH.D., M.D., Ann Arbor, Michigan

Clinical, Histological and Electrical Studies in Muscular Dystrophies
ALEX J. ARIEFF, M.D. and WALTER R. KIRSCHBAUM, M.D., Chicago, Illinois

Gastrointestinal Disturbances Due to Involvement of the Hypothalamus in Bulbar Poliomyelitis
IAN A. BROWN, M.D., Minneapolis, Minnesota

Sequelae of Brain Damage at Birth
H. M. KEITH, M.D., Rochester, Minnesota

Congenital Toxoplasmosis: A Case Report
JOHN MOOSSY, M.D. and HOWARD W. GILLEN, M.D., New Orleans, Louisiana

The Pathologic Anatomy of the Brain in Hemiplegic Cerebral Palsy
HERMAN JOSEPHY, M.D., Chicago, Illinois

Responses of Normal Children to the Face-Hand Test
MAXIMILLIAN FINK, M.D. and MORRIS B. BENDER, M.D., New York City

The Phenomena of Extinction in Spinal Cord Disease
M. F. SHAPIRO, M.D. and D. FELDMAN, M.D., New York City

Business Session 11:40 a.m.
Pearce Bailey, M.D., President, presiding

THURSDAY, APRIL 24, 1952

Afternoon Session 2:00 p.m.
Chairman: Roland P. Mackay, M.D., Chicago, Illinois
Secretary: John S. Garvin, M.D., Chicago, Illinois

Symposium on Pediatric Neurology
"Inability to Walk at the Age of Three Years"

Medical Considerations
DOUGLAS BUCHANAN, M.D., Chicago, Illinois

Pathologic Interpretations
ORVILLE T. BAILEY, M.D., Indianapolis, Indiana

Neurosurgical Aspects
FRANC INGRAHAM, M.D., Boston, Massachusetts

Rehabilitative Procedures
A. B. BAKER, M.D., Minneapolis, Minnesota

Open Discussion of Symposium

FRIDAY, APRIL 25, 1952

Morning Session 9:30 a.m.
Chairman: Morris B. Bender, M.D., New York City
Secretary: Richard P. Schmidt, M.D., Louisville, Kentucky

Neurologic Complications of the Hemorrhagic Diseases
WILLIAM S. CHALGREN, M.D., Mankato, Minnesota

The Problem of Cerebral Phlebothrombosis
JOHN A. WAGNER, M.D., Baltimore, Maryland

Occlusion of the Superior Cerebellar Artery
JOSEPH A. LUHAN, M.D. and SEYMOUR L. POLLOCK, M.D., Chicago, Illinois

Abnormalities of Water and Electrolyte Metabolism
IRVING S. COOPER, M.D., New York City

The Bodily State in Injuries of the Spinal Cord
HERMAN CHOR, M.D., ISIDORE FINKELMAN, M.D. and HERMAN BLUSTEIN, M.D., Chicago, Illinois

Studies on the Cervical Spinal Cord of Man: The Posterior Columns—Sensory Pattern after Interruption
BENJAMIN BOSHES, M.D. and FRANK PADBERG, M.D., Chicago, Illinois

Business Session 11:30 a.m.
Pearce Bailey, M.D., President, presiding

Luncheon Session 12:00 m.

What Are We Going to Do About the Chronic Patient?
HOWARD A. RUSK, M.D., New York City

FRIDAY, APRIL 25, 1952

Afternoon Session 2:00 p.m.
Chairman: Russell N. DeJong, M.D., Ann Arbor, Michigan
Secretary: Claude M. Lowry, M.D., Ann Arbor, Michigan

Preliminary Studies of Sludge Blood in Multiple Sclerosis
L. ROIZIN, M.D., R. ABEL, M.D. and J. WINN, M.D., New York City

Ultracentrifuge Studies on Lipoproteins in the Cerebrospinal Fluid and Serum of Patients with Multiple Sclerosis
R. B. AIRD, M.D., J. GOFMAN, M.D., H. B. JONES, M.D., B. CAMPBELL, M.D. and B. GAROUTTE, M.D., San Francisco, California

The Natural History of Cerebral Infarcts
CLARK H. MILLIKAN, M.D., Rochester, Minnesota

Arteriovenous Malformations of the Brain
CARL F. LIST, M.D., Grand Rapids, Michigan

Remainder of afternoon session given to papers sponsored jointly by the American Academy of Neurology and the American League Against Epilepsy.

Papers Read by Title

Two Cases of Muscular Dystrophy
IRVING C. SHERMAN, M.D. and LOUIS D. BOSHES, M.D., Chicago, Illinois

Cervical Protruded Intervertebral Discs: An Analysis of Postoperative Results
KENNETH H. ABBOTT, M.D. and JAMES R. GAY, M.D., Columbus, Ohio

Platelet Adhesive Index Studies in Multiple Sclerosis and Other Neurological Disorders
MORTON NATHANSON, M.D. and PHILIP SAVITSKY, New York City

Investigation of Pyromen as an Agent in the Treatment of Neurologic Disease
ALLAN A. BAILEY, M.D., Rochester, Minnesota

Some Commonly Overlooked Neurologic Syndromes in Children
HAROLD STEVENS, M.D., Washington, D. C.

The Withdrawal Syndrome in Organic Brain Disease
EDWIN A. WEINSTEIN, M.D., New York City

Neurology

.....BOOK REVIEWS....

Modern Trends in Neurology

Anthony Feiling, M.D., F.R.C.P., Editor. 1951. New York: Paul B. Hoeber, Inc., 717 pages.

It is generally agreed that the present-day output of medical literature throughout the world has become so vast that it is virtually impossible for any busy worker, even the specialist, to keep abreast of latest developments. The aim of this book has been to help the neurologist and the postgraduate student by condensing herein some of the more interesting and valuable additions to the science and practice of neurology which recent years have produced. The individual collaborators are in the main from the distinguished British school of neurology, but three of the twenty chapters are by well-known American colleagues.

The first chapter, on "Conduction of the Nervous Impulses," introduces an important subject which is rarely mentioned in the ordinary textbook of neurology. The lengthy discussion of "The Frontal Lobes and Their Functions," by Dr. Denny-Brown, includes not only a full and up-to-date account of previous work and opinions, but also new and original matter on a subject of vital importance and particular interest at the present time. Drs. Kunkle and Wolff, in their section on "Headache," summarize their important contributions in this field, as does Dr. Mixter in his chapter on "Rupture of the Intervertebral Disc."

The sections on "The Cerebral Palsies of Infancy" by Dr. William C. Wyllie, "Abscess of the Brain" by Dr. Joe Pennybacker, "Intracranial Tumours" by Mr. D. W. C. Northfield and Dr. Dorothy Russell, "Intracranial Aneurysms" by Dr. S. P. Meadows, "Nervous and Vascular Pressure Syndromes of the Thoracic Inlet and Cervicoaxillary Canal" by Dr. F. M. R. Walshe, "Clinical Electroencephalography" by Dr. Denis Williams, and "Diagnostic Neuroradiology" by Dr. J. W. D. Bull are all extremely valuable contributions.

This book does not, nor does it claim to, present a complete review of all aspects of neurology. But those that it does cover are dealt with in a comprehensive and extremely up-to-date manner. Many references to publications of 1949 and 1950 are cited—which is a pleasant surprise in a volume of this size and scope. In the discussion of myasthenia gravis, however, even though the organic anticholinesterase compounds are mentioned, there is no reference to ACTH, and in the section on epilepsy some of the newer drugs are not included. The American reader, furthermore, may take issue with certain statements. In the discussion on neurosyphilis it is

stated "In view of the percentage of failures with penicillin alone and at the same time appreciating its extreme value as a therapeutic agent, many syphilologists reverted to the use of arsenicals and bismuth in addition to penicillin for the treatment of early syphilis." And in the section on poliomyelitis, while a middle road is taken between complete inactivity and activity in the treatment of the acute stage, the former principle is stressed, and the statement is made "After the first week each joint should be passively moved through a full range once, and later twice, daily." In spite of the above minor criticisms, however, the book must be regarded as an excellent survey of current advances in neurology. R. N. DEJ.

Studies in Lobotomy

Milton Greenblatt, M.D., Robert Arnot, M.D. and Harry C. Solomon, M. D. 1950. New York: Grune and Stratton, Inc., 495 pages, $10.00.

The editors of this book should have dedicated it to "affectionate Becky and Crotchety Old Maid Lucy", for these two Yale chimpanzees with frontal lobe ablations started Egaz Moniz thinking. The result of his venture was revolutionary in the treatment of mental disease, and prefrontal lobotomy and its modifications are now acceptable procedures.

The Boston Psychopathic Hospital group with elaborate caution have employed the procedure for selected patients from Massachusetts Mental Hospitals since 1943. More than 500 patients have been studied with critical analyses of over 200. *Studies in Lobotomy* reviews the results of these carefully planned observations. Editors Greenblatt, Arnot and Solomon have had the assistance of 27 contributors, many of them members of the staff of the Boston Psychopathic hospital, others from Boston medical schools.

The scope of the study can best be presented by referring to the content of some of the chapters. After the introductory chapter by Solomon, Greenblatt has brought psychosurgery up to date in a well documented review of the literature. Surgical technics and considerations cover two chapters. Postoperative behavior is described and summarized in a chapter by Rose and there is a short chapter on nursing and procedure and problems. A considerable portion of the remainder of Part I is given over to the evaluation of frontal lobotomy as a therapeutic procedure for 205 patients operated upon prior to 1947. This follow-up study includes detailed clinical and sociologic observations and statistical analyses. The following are some of the important topics receiving special attention: changes in signs and symptoms, hospital adjustment, work adjustment, family adjustment and community adjustment. Diagnostic catagories, pre-illness personality traits, mental status and personality traits during the illness, were carefully analyzed in terms of their predictive value for the success of the procedure.

There is a provocative chapter on the results of unilateral and bimedical lobotomy. This is a "pilot study" of patients with fractional sections of frontal tracts—unilateral and bilateral. The adoption of this modification would meet the predictions of Fulton, who has said that from his knowledge

of animal behavior after selective localized lesions, he believes that changes desired could be accomplished by the section of the medially disposed tracts (inferior medial quadrant). Indications from the Boston study (at the time of writing—14 patients had had bimedial sections) predict therapeutic usefulness of partial operations.

Taking advantage of their opportunity to correlate clinical findings with modern knowledge of neurophysiology and neural anatomy derived from the research laboratory, the authors made careful observations of frontal lobe functions before and after psychosurgery. Part II is concerned with these observations. One valuable chapter concerns the anatomical changes in six patients who died from 11 to 235 days after operation. There are detailed drawings and photomicrographs to show the planes of the surgical transections and extent of surgical destruction and degenerative changes secondary to interruption of the various fiber tracts and their neuclei. In the summary of this valuable chapter, authors Yakovlev, Hamlin and Sweet point out that most studies made of lobotomized subjects in attempts to correlate behavioral changes have stressed the degeneration in the anterior thalamic tracts and nuclei to the "exclusion of obvious degeneration of far greater mass of efferent projections which connect the frontal lobes to all the levels of the neuroaxis. . . ." In words of the authors, "these efferent projection systems are equally important and must be taken into consideration in the construction of a valid conceptual schema of the anatomico-clinical correlation between the frontal lobotomies (and other injuries of the brain) and the reorganization of behavior which follows them."

Other chapters report well planned observations of behavior and autonomic functions and include the following topics: Changes in cerebral spinal fluid after lobotomy, relation of frontal lobe to the autonomic nervous system, the effect of lobotomy and electrical stimulation of the orbital surface of the frontal lobes upon respiration and blood pressure, lobotomy and urinary function, skin temperature changes after unilateral and bilateral prefrontal lobotomy, and measurement of motor withdrawal reaction following operation. In a chapter on electroencephalographic and clinical effects of the operation special consideration is given postlobotomy convulsions. Psychometric changes are evaluated and a description is given of an attempt to set up a sociometric scale to evaluate behavioral changes. The occupational therapist plays an important role in the rehabilitation of the lobotomized patient. In a chapter on this subject these workers stress the importance of knowing the patients and their interests before lobotomy and early application of these aids following surgery.

Solomon has summarized succinctly the postoperative behavioral changes and points out the indications by symptoms and nosological disorders for psychosurgery.

This volume will be a welcome reference for all who wish answers to almost any question regarding lobotomy. It is, in fact, a collection of studies by persons specialized in each of the several fields, a well integrated and worthy demonstration of the consideration of the whole patient in his entire setting. It is a fine example of cooperation among psychiatrists, neurologists, neurosurgeons and their ancillary workers. M. G. M.

Problems in Cerebellar Physiology

G. Moruzzi, M.D. 1950. Springfield, Illinois: Charles C Thomas, Publisher, 116 pages, $3.25.

In this scholarly monograph are published a series of lectures on cerebellar physiology delivered by Dr. Moruzzi at the Northwestern University Medical School in December 1948, together with a summarizing chapter. It deals in the main with the anterior lobe, and presents a critical survey of the results of recent investigations of the function of this portion of the cerebellum. Moruzzi states that the position of the anterior lobe in the physiology of the cerebellar cortex is comparable to that of the sensory-motor area in its relations to the cerebral cortex. Both receive somesthetic impulses and both influence the activity of spinal cord motor neurons; in both cases somatotopic localizations have been found in the excitable areas. The inhibitory influence of this organ on postural tonus has long been known, but it is now revealed that facilitation of tonus can also be obtained by appropriate stimulation of the so-called inhibitory area. Furthermore, this lobe receives corticopontine impulses, projects to the sensory-motor cortex, and facilitates cortical activities at a cerebral level. The inhibition of spinal motor neurons represents only one aspect of the activity of the anterior lobe—the function of this area can be described as one of regulating, through facilitation and inhibition, spinal, brain stem, and cortical centers.

In view of the fact that our concepts of the physiology of the cerebellum are undergoing drastic changes at the present time (as a result of the work of Moruzzi, Snider, and others), this little book may come to be regarded as an important milestone of neurophysiology.

R.N.DeJ.

Diseases of The Nervous System

W. Russell Brain, M.D. 1951. London: Oxford University Press, 1002 pages, $8.50.

The fourth edition of this well-known English textbook of clinical neurology has both the virtues and faults of its earlier editions. It is comprehensive, methodical, and generally accurate and abounds in excellent thumb-nail sketches of individual diseases, pared down to the bare essentials. The content of the work appears to represent a painstaking compilation and digest of what has been established and accepted, both old and new. There is little, perhaps too little, evidence of personal bias. In these respects the book will serve admirably as a brief reference work for the medical student and the practitioner. A full and well arranged table of contents adds to this kind of usefulness.

To achieve so wide a scope in a volume of this size has, however, required compression of material, so great in many places as to squeeze it almost dry of interest and sometimes even of value. Almost everywhere one feels this cramping effect. For example, little help is given to the problem of the treatment of intracranial aneurysms by merely declaring that the risk of surgical procedures must be balanced against the risk of further hemorrhage without indicating

something of the magnitude of those risks. Scant attention is paid to the symptomatology, pathology or treatment of bulbar poliomyelitis. The subject of herniation of lumbar intervertebral discs is well presented, but cervical disc disease is barely mentioned, especially that frequent simulator of degenerative spinal cord disease, the midline cervical disc. A very well conceived exposition on the nature of epilepsy also suffers from brevity imposed upon it. A short but well chosen and representative bibliography compensates in part for what is wanting in the text.

Aside from brief new sections (not exceeding three pages in all) dealing with leptospiral meningitis, temporal arteritis, infectious mononucleosis, and compression of the median nerve in the carpal tunnel, the present edition does not differ appreciably from the previous one except in some fields of treatment. The most important revisions in this regard concern the therapy of tuberculous and other forms of meningitis and of neurosyphilis. One is gratified to find that the author ignores certain fads in the treatment of multiple sclerosis currently in vogue in this country, but is surprised to note a more archaic but equally useless remedy, arsenic. Other anachronisms appear here and there in an otherwise up-to-date treatise. Few would any longer agree that the rubrospinal tract is the principal route by which the cerebellum influences the lower motor neuron in man, that subtemporal or suboccipital decompression is the procedure of choice in the management of inoperable brain tumor, or that penicillin must be given intrathecally in the treatment of meningitis.

Nevertheless, the book is a good one for its purposes. If, like many another good textbook, it is a body without a soul, one can say that the body is a sound and healthy one, all in all.

R. B. R.

Causalgia

Frank H. Mayfield, M.D. A monograph in American Lectures in Neurosurgery. 1951. Springfield, Illinois: Charles C Thomas, Publisher, 65 pages, $2.25.

This monograph is a straightforward clinical account of causalgia based largely on the author's personal experiences. The incidence, symptomatology, signs, differential diagnosis and surgical treatment are discussed. The author has found injection of the sympathetic nerve trunks of little therapeutic value. The use of sympathetic blocking agents, which are becoming more numerous and effective, is very briefly mentioned for the author believes that, with rare exceptions, surgical sympathectomy is required in the treatment of causalgia. The surgical techniques are described with the aid of good illustrations. Brief references are made to the pertinent literature. The format of the book is pleasing; the illustrations are well done.

This monograph is not an exhaustive treatise on causalgia, but it does present a clinical summary of the subject which the medical student or general practitioner should appreciate.

A. E. W.

Neurology

Clinical Significance, Histopathology and Classification of Cerebral Swelling

I. Mark Scheinker, M.D.

IN THE vast majority of cases of space-consuming lesions, increased intracranial pressure is the direct result of cerebral swelling. General brain tumor symptoms such as headache, vomiting and dizzy spells, associated with general signs of increased intracranial pressure (papilledema and bradycardia), often are the result of cerebral swelling. Neurosurgeons have long realized that cerebral swelling is the greatest obstacle to exact localization of brain tumors. Moreover, the presence of swelling may at times be of greater significance for postoperative prognosis than is the structural character of the tumor itself.

The appalling frequency of cerebral swelling in neurosurgical practice dealing with brain injuries gives an additional practical significance to the study of this condition. The paucity of histopathologic studies concerning the problem of cerebral swelling is surprising. Moreover, the terms cerebral swelling and cerebral edema are used by both clinicians and pathologists with quite different connotations. There is great diversity of opinion as to what histologic changes characterize cerebral swelling. Until relatively stable histopathologic definitions are established, this confusion will persist.

DEFINITION AND TERMINOLOGY

A thorough study of a large number of cases seems necesssary to bring order out of the diversity of opinions and findings relating to the pathology and pathogenesis of cerebral swelling and edema. After many years of systematic investigation of the problem, the following conclusions were reached.

From the department of neuropathology, University of Cincinnati College of Medicine.

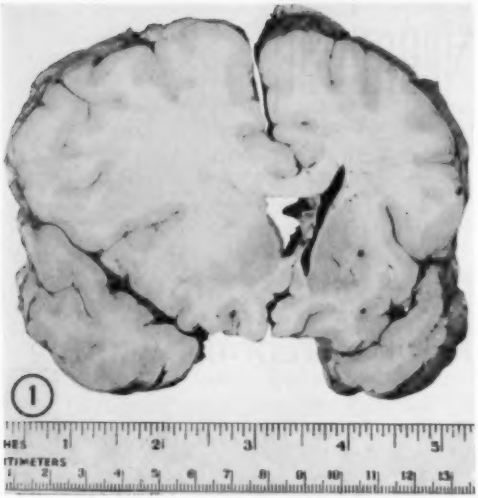


FIG. 1. Swelling of the right hemisphere produced by a small carcinoma metastasis of the right frontal lobe. Note the increase in bulk of the white matter, shift of the midline structures and displacement of both lateral ventricles to the left.

"Cerebral swelling" is the term proposed to denote the gross appearance of a brain characterized by a local or diffuse increase in bulk of one or both hemispheres, regardless of the underlying histopathologic findings.

The gross findings of cerebral swelling are characterized by: (1) increase in brain volume; (2) flattening of the gyri and narrowing or obliteration of the sulci; (3) enlargement of the central and subcortical white matter with consequent narrowing and compression of the cortical gray; (4) loss of demarcation between white and gray matter; (5) decrease in size or complete obliteration of one or both lateral ventricles; and (6) shift of the midline structures and of the third ventricle from the side of the cerebral swelling toward the opposite hemisphere when the swelling is unilateral (figure 1).

It is proposed that the condition referred to grossly as cerebral swelling is represented microscopically by three underlying histopathologic syndromes which can be designated as (1) tumefaction (stage 1), (2) edema (stage 2), and (3) liquefaction (stage 3).

It is quite evident that fundamentally they represent three different stages of the same biologic process; occasionally these stages may merge insensibly with one another. The three conditions can be differentiated histologically.

CEREBRAL TUMEFACTION

Microscopic findings characteristic of cerebral tumefaction may be overlooked easily in routine sections stained with hematoxylin and eosin. They are best noted with careful study of silver impregnations such as Bodian or Bielschowsky stains.

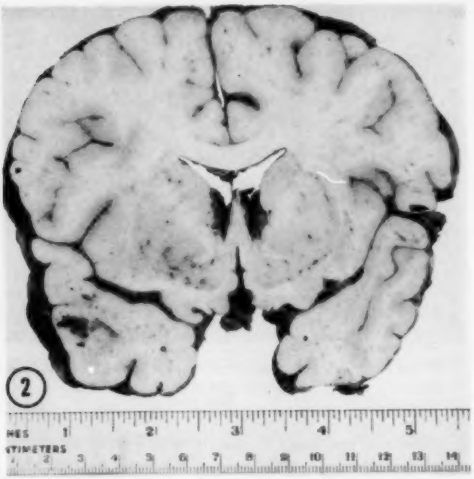


FIG. 2. Swelling of the central and subcortical white matter of both hemispheres. Note the loss of demarcation between white and gray matter.

Pertinent histologic findings characteristic of cerebral tumefaction may be summarized thus: (1) *parenchymatous changes* with evidence of swelling of the nerve fibers, myelin sheaths, glia, and particularly of the oligodendroglia; (2) *vascular alterations* confined to the small veins and capillaries, characterized by congestion and stasis and by swelling and degeneration of the endothelial cells. These changes are predominant in the white matter; they seldom extend into the gray substance.

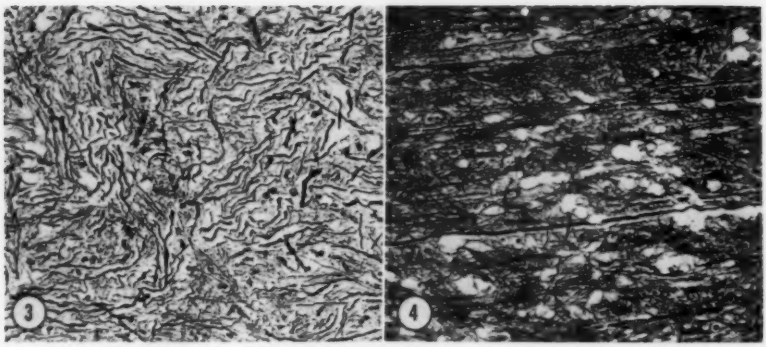
A typical instance of this initial stage of cerebral swelling, occurring in association with brain injury, is cited.

Case 1.—M. B., a 28 year old white woman, was admitted to the hospital one hour after she fell down a flight of steps. On admission to the hospital she was unconscious and gasping for breath. The pupils were fixed to light and maximally dilated. The optic disks were not remarkable. There was flaccid paralysis of all extremities; the tendon reflexes were not obtainable. The neck was supple; there were no signs of meningeal irritation. Roentgenograms of the skull revealed a linear occipital fracture extending into the base.

Shortly after admission all deep reflexes returned and were hyperactive on both sides. A few minutes later Cheyne-Stokes respiration developed and then suddenly ceased. For the following 38 hours the patient was maintained in a Drinker respirator. During this period her blood pressure fell to 80/60, and remained low in spite of seven units of plasma and two blood transfusions. Spinal puncture showed a pressure of 290 mm. of water and grossly bloody fluid. The patient died 39 hours after admission to the hospital.

Examination of the Brain.—Upon reflection of the dural cap, there was found over the right parietal region near the midline a blood clot measuring approximately 17 mm. in thickness. Under the left dural leaf there was a minimal amount of clotted blood.

The brain showed pronounced increase in bulk of both hemispheres with considerable flattening of the gyri and narrowing of the sulci. There was generalized congestion of the smaller and larger pial veins.



FIGS. 3 and 4. Diffuse swelling and irregular outline of the nerve fibers of the white matter. Bodian silver impregnation.

The undersurfaces of the frontal lobes and the tips of both temporal lobes revealed signs of contusion, with a tear of the brain surface along the course of the second temporal convolution extending backward for a distance of about 5 to 6 centimeters. The cerebellar hemispheres likewise showed signs of contusion limited chiefly to their inferior and lateral aspects. Bilateral uncal herniations were somewhat more pronounced on the left than on the right.

Coronal sections through both hemispheres (figure 2) revealed definite swelling of the central and subcortical white matter of both hemispheres, associated with a considerable loss of the characteristic demarcation between gray and white matter, particularly noticeable in the second and third frontal lobe convolutions of the right hemisphere. Both lateral ventricles appeared somewhat small and compressed by the swollen white matter.

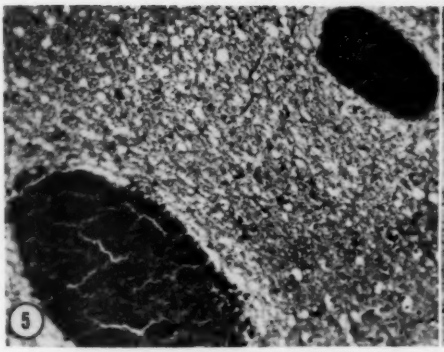
There was some evidence of diffuse congestion of the corona radiata and the basal ganglia. In the right temporal lobe there were numerous coalescent petechial hemorrhages. In addition, there was a recent softening in the lowermost portion of the head of the left caudate nucleus, involving the lateral wall of the ventricle and extending toward the medial portion of the left internal capsule.

The cerebellum and brain stem disclosed congestion and numerous scattered petechial hemorrhages. Both dentate nuclei showed evidence of an early stage of hemorrhagic softening.

Microscopic examination of sections taken from several areas of both hemispheres, basal ganglia, hypothalamus, brain stem and cerebellum disclosed two principal types of alterations, (a) parenchymatous changes and (b) vascular alterations.

(a) Parenchymatous changes:—Preparations stained with hematoxylin and eosin failed to reveal any abnormalities other than a slight degree of tissue rarefaction and congestion, and stasis of the small veins and capillaries with occasional perivascular hemorrhages. Careful analysis of sections impregnated with silver (Bodian stain), however, disclosed a considerable swelling of most of the nerve fibers of the white matter (figures 3 and 4). More advanced changes are indicated by irregular, ragged outlines of some of the larger axis cylinders and by the formation of numerous varicosities and end-bulbs. The most obvious swelling of the nerve fibers is noted in sections taken from the central white matter.

Less obvious than those in the axis cylinders, changes of the myelin sheaths consisted of diffuse, irregular swelling and beading of the large majority of myelin sheaths. In sec-



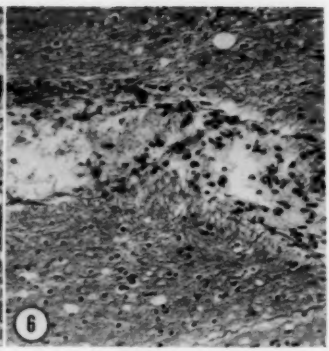


FIG. 5. Vascular alterations. Note the extremely distended capillaries and small veins displaying signs of congestion and stasis. Hematoxylin-eosin stain.
FIG. 6. Hypertrophic and hyperplastic changes of the capillary endothelium. Hematoxylin-eosin stain.

tions taken from the white matter there is diffuse pallor of the tissue, with many sheaths unstained and widely separated from each other.

In preparations stained with cresyl violet there was occasional swelling or loss of stainability of some of the nerve cells. These nerve cell alterations were especially noticeable in sections taken from the medulla and cerebellum. The cells of the inferior olive, which were severely damaged, showed signs of swelling and chromatolysis. In some areas only a pale, unstained silhouette of the individual cells remained. Only a small portion of the right olive was relatively well preserved. The cells of the dentate nucleus revealed changes similar to those found in the olives. There were present, too, all stages of ischemic degeneration, beginning with swelling and chromatolysis and ending with shrinkage, homogenization or complete loss of stainability and formation of ghost cells.

The cerebellar cortex showed a selective destruction of the granular layer; the Bergmann's glia and the Purkinje cells were well preserved.

Changes of the glia were less conspicuous. There was, however, a moderate degree of swelling of most of the oligodendroglia cells. Some of the cells had a large oval, swollen nucleus and rounded cytoplasm harboring numerous fine granules. The astrocytes appeared to be little affected. There were no signs of microglial proliferation.

(b) Vascular alterations:—The distended capillaries and small veins showed signs of congestion and stasis (figure 5). Many of the small vessels were surrounded by small accumulations of extravasated red blood cells.

Very striking were the hypertrophic and hyperplastic changes of the capillary endothelium (figure 6). The nuclei of the endothelial cells were markedly swollen and the surrounding cell protoplasm occasionally contained a few vacuoles. Many of the capillaries were conspicuous for the increased cellularity of their walls. Actual infiltration with hematogenous cells, however, was not present. Definite signs of degenerative alterations of the capillary endothelium were seldom seen.

CEREBRAL EDEMA

Whereas parenchymal changes in the early stage of cerebral tumefaction may be easily overlooked unless analyzed with special staining methods, the

more advanced changes of cerebral edema are quite conspicuous in preparations stained with the routine hematoxylin eosin stain.

Histologic differentiation between the two conditions is relatively simple. Essential criteria for cerebral edema are specified as follows: (a) alveolar or sieve-like appearance of the nervous tissue; (b) maximal distention of the perivascular and pericellular spaces; (c) signs of venous congestion and stasis; and (d) evidence of degeneration and necrosis of the endothelium of the capillaries.[1]

It should be emphasized, however, that despite the histologic differences between cerebral tumefaction and cerebral edema, the two conditions are but two stages of the same biologic process. The relatively slight, early lesions of cerebral tumefaction indicate the possibility of a reversible process, whereas the more advanced, severe changes characterizing cerebral edema appear to be irreversible.

There is little doubt that cerebral edema is to be considered as an advanced stage of cerebral tumefaction. The histopathologic process characterizing cerebral tumefaction apparently is the result of an intracellular hydration with consequent swelling of the individual cells and fibers. This process of physicochemical hydration is histologically apparent only when it has attained a certain degree of intensity (which may explain the absence of structural findings, as reported by many workers). The initial stage of intracellular hydration, however, is soon followed by extracellular fluid accumulation together with a tremendous increase of tissue fluid within the interstitial, pericellular and perivascular spaces, resulting in the histopathologic changes characteristic of cerebral edema.

A typical case of cerebral edema associated with brain tumor is cited.

Case 2.—E. S., a 58 year old white woman, was admitted to the hospital with a history of generalized epileptic seizures throughout the preceding three years. During the last six months a steadily increasing speech disturbance had been noted.

On admission the patient was found to be disoriented and slightly confused. The following pertinent neurologic findings were noted: slight right-sided facial weakness associated with mild paresis and tremor of the right arm, and rigidity in both legs, more marked on the right.

Laboratory data.—A lumbar puncture yielded clear, colorless cerebrospinal fluid under pressure of 250 mm. of water; it contained no cells; the total protein content was 240 mg. per 100 cc., and the Wassermann reaction was negative.

Roentgenograms of the skull showed increased vascularization, especially pronounced in the left frontoparietal region. Ventriculograms disclosed a marked shift of the lateral ventricles to the right, the shift being most evident in the frontal region; the left temporal horn appeared considerably smaller than the right. The third ventricle, though tilted sharply, was visible as a straight line.

Six days following admission a parietal flap was turned, with resulting massive bleeding from the scalp, bone and dura which were highly vascularized. A large infiltrating glioma was found in the left posterior frontal region. Its partial removal was followed by an acute increase of cerebral swelling, the presence of which had been preoperatively indicated, at least to some degree, in the ventriculograms.

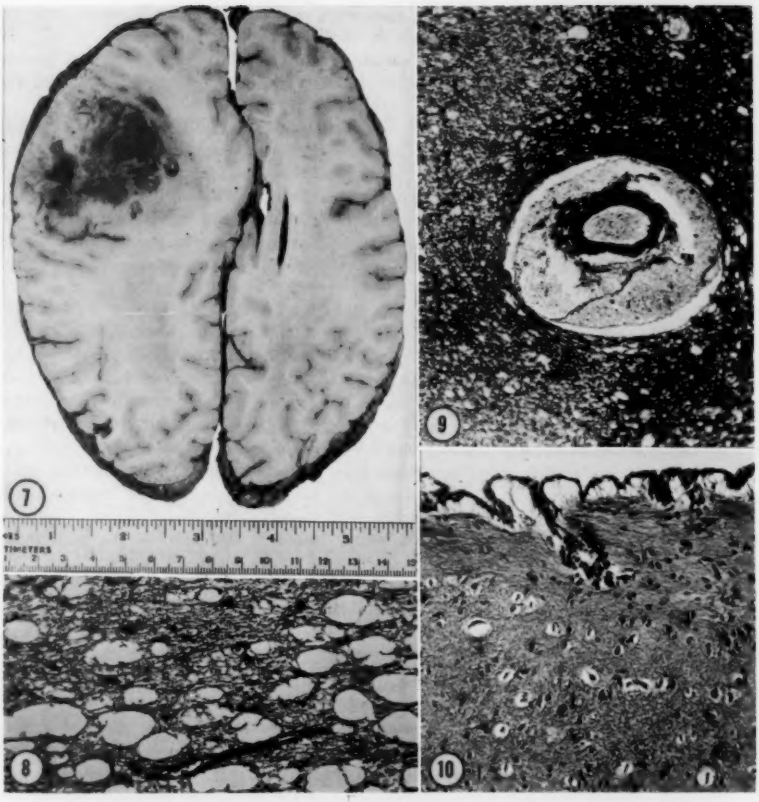


FIG. 7. Increase in bulk of the anterior two-thirds of the left hemisphere. Note the circumscribed area of cyst formation surrounded by a narrow zone of neoplastic tissue.

FIG. 8. Spongy appearance of the white matter caused by distention of the pericellular and perivascular spaces. Hematoxylin-eosin stain.

FIG. 9. Vascular alterations characteristic of vasoparalysis. Note the degeneration of the vessel wall associated with increased permeability for serous fluid. Hematoxylin-eosin stain.

FIG. 10. Accumulation of fluid between the pial end of the underlying cortical gray matter, thus forming an artificial "subpial space." Cresyl violet stain.

It is of interest to note that, during the operation, two or three medium-sized cortical blood vessels and one fair-sized vessel in the tumor bed had to be clipped.

The patient's postoperative course was critically stormy. A few hours after the operation the blood pressure rose steadily to a systolic level of 170 (the preoperative systolic level had been 130). About three hours after the operation the patient stopped breathing; she was immediately taken to the operating room where the flap was reflected and relatively

small postoperative extra- and intradural clots were removed. The brain, which was extremely edematous, was herniating through the skull defect.

Immediately following operation the patient was given 50 cc. of 50 per cent sucrose without obvious benefit, and was placed in an artificial respirator. Death occurred the following morning.

Examination of the brain.—On gross examination the brain, as viewed from above, showed a tremendous degree of cerebral herniation through the region of the dural defect; the protrusion measured up to 3 cm. and corresponded to the 8 cm. opening in the dura. The gyri throughout both hemispheres were flattened and the sulci obliterated. The leptomeninges of the left hemisphere showed evidence of subarachnoid bleeding. Inspection of the median cleft disclosed an extreme degree of herniation and displacement of the mesial portion of the left hemisphere under the falx, with corresponding indentation of the mesial face of the right hemisphere.

The undersurface of the left frontal lobe showed a considerable increase in bulk and evidence of a shift of the midline to the right. In addition, there were signs of a well defined transtentorial herniation of the left temporal lobe and of a cerebellar pressure cone.

Horizontal sections through both hemispheres disclosed a tremendous increase in bulk of the anterior two-thirds of the left hemisphere and a circumscribed area of cyst formation lying within the tumor bed (figure 7). There were likewise a striking shift of the ventricular system and compression of the left lateral ventricle.

Microscopic examination of sections taken from different portions of the centrum semiovale and from the subcortical white matter of the swollen left hemisphere disclosed both diffuse alterations of the nervous parenchyma and vascular changes. Figure 8 illustrates the characteristic spongy appearance of the tissue caused by distention of the pericellular and perivascular spaces and by numerous large, oval spaces filled with serous fluid. The latter contained neither cellular elements nor stainable substance.

In preparations stained by the Bodian silver method the widely separated nerve fibers displayed advanced degenerative changes, such as irregularity of contour, beading and final loss of stainability.

The Loyez staining method for myeline sheaths revealed a striking, diffuse pallor. The lack of stainability was due partly to separation of the myelinated fibers and partly to the considerable degree of myelin sheath degeneration, as characterized by pronounced irregularity of contour and occasional disintegration into numerous darkly-stained globules and granules.

The glia showed only minor alterations. Some of the astrocytes disclosed various degenerative changes of their nuclei. There was no appreciable increase in number of the neuroglial fibers. The oligodendroglial cells were moderately swollen and showed partial loss of stainability; in some of their nuclei the chromatin was broken up into fine granules. The microglial cells were little affected. A few microglial phagocytes were seen near the walls of some of the blood vessels.

The axons and myelin sheaths of the overlying cortical gray matter were relatively well preserved. The nerve cells, however, showed various stages of ischemic degeneration as a result of tissue hypoxia, secondary to circulatory disturbances.

The vascular alterations, which were conspicuous, consisted of pronounced congestion, stasis and morphologic signs of vasoparalysis. Most of the veins and capillaries exhibited distention of their lumina and varying degrees of degeneration of the walls, associated with increased permeability for serous fluid (figure 9). The perivascular spaces were tremendously distended with fluid. In sections taken from the neighborhood of the tumor cyst, the veins of the white matter were extremely distended and engorged with blood. Frequently they were surrounded by dense cuffs of extravasated red blood cells. In addition there were a few coalescent, diapedetic hemorrhages in the white matter.

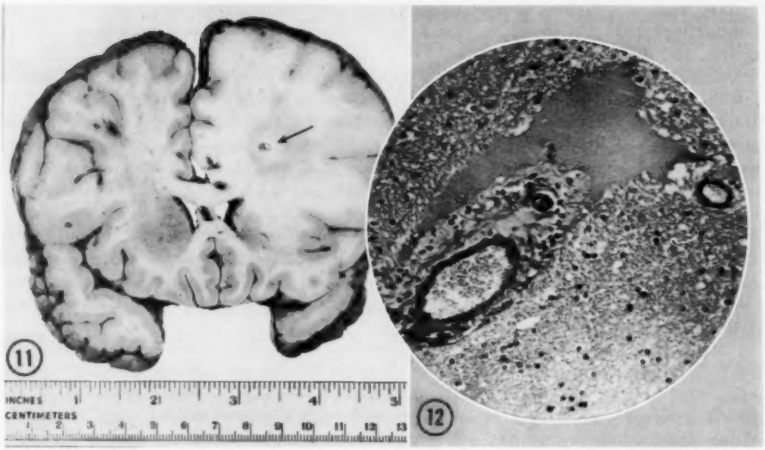


FIG. 11. Swelling of the left hemisphere. Note the small circumscribed abscess in the central portion of the white matter on the left.

FIG. 12. Liquefaction of the cerebral tissue associated with accumulation of serous fluid throughout the liquefied parenchyma and within the distended perivascular spaces. Hematoxylin-eosin stain.

It is of interest to note that in some areas there was an accumulation of fluid between the pia and underlying cortical gray, thus forming an artificial "subpial space" (figure 10). A similar accumulation of fluid was noted in the vicinity of some of the blood vessels between the pial-glial membrane of the perivascular space and the subadjacent nervous tissue.

CEREBRAL LIQUEFACTION

This last, most advanced stage of cerebral swelling is characterized by: (1) large accumulations of serous fluid within the central white matter; (2) diffuse and almost complete disintegration of the nerve fibers and myelin sheaths; (3) regressive glial changes (Alzheimer's ameboid glia); and (4) degenerative alterations of the vessel walls.

A typical instance of cerebral liquefaction is cited herewith.

Case 3.—W. A., a 45 year old man, was admitted to the hospital with the diagnosis of cystic bronchiectasis. On February 15, 1945, a left-sided tonic clonic convulsion occurred followed by weakness of the left arm. Neurologic examination revealed normal findings except for an Oppenheim sign on the left.

Lumbar puncture showed a pressure of 160 mm. of water; the fluid contained 2 lymphocytes per c. mm., 60 mg. per 100 cc. of sugar, and 695 mg. per 100 cc. of chloride.

On February 13 bronchoscopy disclosed large accumulations of purulent material within the left bronchi. On March 10 a left total pneumonectomy was performed. The postoperative course was uneventful except for occasional left-sided tonic-clonic convulsions. Four weeks after the operation the patient became drowsy and lethargic, and showed signs of a left-sided hemiparesis.

On April 9 right frontal, right temporal and bilateral occipital burr holes were made, but the suspected brain abscess was not located. The patient developed signs of decerebrate rigidity and died the following day.

Examination of the Brain—The brain appeared grossly swollen, the gyri being flattened and the sulci almost obliterated. The pial veins were extremely congested.

In the right postcentral gyrus about 2 cm. from the midline there was a small circumscribed area of brownish discoloration, soft to touch, which appeared to represent an underlying abscess. Inspection of the median cleft showed a herniation of the supracellosal gyrus from left to right. The ventral surface of the brain showed bilateral uncal herniation.

Coronal sections through both hemispheres revealed a striking degree of swelling of the entire left hemisphere and a small circumscribed abscess in the central portion of the white matter on the left (figure 11). The demarcation between white and gray matter appeared ill defined; both lateral ventricles were small and slightly shifted to the right.

On further examination a second sharply demarcated, small abscess was found in the right parietal lobe.

Microscopic examination of sections taken from the white matter of the swollen left hemisphere disclosed an extreme degree of tissue liquefaction. Large accumulations of serous fluid were seen within the extremely distended perivascular spaces and free throughout the liquefied parenchyma (figure 12).

Preparations impregnated by the Bodian silver method revealed an almost complete destruction of the nerve fibers or disintegration into small fragments. The remaining axons, separated from one another by large spaces, exhibited various degrees of degeneration ranging from tortuosity and diffuse or varicose swelling to complete disappearance.

Sections stained by the Loyez method for myeline sheath revealed diffuse pallor of the white matter as a result of widespread disintegration of most of the myelin sheaths.

The glia showed far advanced regressive changes characteristic of Alzheimer's type of ameboid glial degeneration. The individual glial nuclei were shrunken and pyknotic, and were surrounded by scanty, irregularly shaped cytoplasm.

The majority of small veins showed necrosis and homogenization of their walls.

Sections taken from the cortical ribbon disclosed signs of compression and diffuse ischemic changes of the nerve cells.

GENERAL PATHOLOGIC CONSIDERATIONS

Among the histologic findings characteristic of all three stages of cerebral swelling (cerebral tumefaction, cerebral edema and cerebral liquefaction), circulatory changes are uniformly essential and predominant.

The earliest stage of vascular alterations found in cerebral tumefaction consists of a striking swelling of the endothelial cells of the capillaries.

A more advanced type seen in cerebral edema reveals circulatory disturbances characterized by an extreme degree of congestion and stasis in frequent association with signs of vasoparalysis. These vascular changes, confined chiefly to small veins and capillaries, are manifested by signs of increased permeability for serous fluid of the vessel walls.

Finally, in cerebral liquefaction the smaller veins and capillaries disclose frank signs of degeneration and necrosis.

The pathophysiologic significance of these widespread circulatory disturbances, which result in increased outflow of fluid from the blood vessels into the tissue spaces, will be discussed later.

Alterations of the nervous tissue proper, secondary to the circulatory disturbances, are briefly summarized as follows: In cerebral tumefaction, diffuse swelling of all constituents of the nervous parenchyma is the predominant, characteristic feature. Such changes are observed only rarely in cases of cerebral edema. The latter is characterized by an alveolar or sieve-like appearance of the nervous tissue, together with maximal distention of the perivascular and pericellular spaces.

Whereas the myelin sheaths and nerve fibers in cerebral edema disclose only a relatively moderate degree of degeneration, in cerebral liquefaction the bulk of the nervous parenchyma shows severe damage or complete destruction. Even the glia, which seems to withstand the process of tumefaction and edema quite well, succumbs to the process of liquefaction, disclosing widespread regressive signs in the form of Alzheimer's ameboid glial degeneration.

From these points of differentiation, it seems proper to conclude that cerebral liquefaction is a late sequela of cerebral tumefaction and cerebral edema. There is little doubt that the three histopathologic syndromes are varieties of the same morbid process. Differences in their morphology may be explained by differences in the duration and severity of the causative agent. Whereas the pathologic process in the early stage of cerebral tumefaction may be interpreted as intracellular accumulation of fluid with consequent swelling of the individual cells and fibers, the more advanced changes of cerebral edema and cerebral liquefaction are probably caused by an extracellular increase of tissue fluid within the interstitial spaces. And it is to this condition that the differences among the histologic pictures of the three stages of cerebral swelling are to be attributed. Needless to say, the borderline between one stage and the next is not always well defined. In many cases there is gradual transition or partial overlapping from one to another of the three stages.

It should be stressed that the relatively minor lesions observed in cerebral tumefaction indicate the possibility of a reversible process, whereas the more advanced lesions seen in cerebral edema and cerebral liquefaction appear irreversible.

Regardless of the histopathologic varieties of the morbid process, the gross appearance of the brain always manifests a considerable increase in bulk (actual swelling) of one or both hemispheres. The most appropriate common designation of the gross appearance of all three varieties of the morbid process, therefore, would seem to be cerebral swelling.

Predominant localization of cerebral swelling. The white matter is predominantly involved in all cases of brain swelling. The cerebral gray matter (cortical gray and basal ganglia) is less vulnerable. Although pathologic lesions of the cortical ribbon are frequently seen, they differ considerably from those of the white matter. Even grossly there is a striking discrepancy between the two. In contrast to the tremendous swelling of the white matter, the corti-

cal gray substance is considerably decreased in size and may appear narrowed and compressed.

Microscopically the change most commonly observed in all three stages is early chromatolysis of the nerve cells. More advanced changes, such as pyknosis or ischemic nerve cell degeneration are encountered only occasionally. The latter is characterized by loss of stainability of the cell cytoplasm, shrinkage of the nucleus, and irregularity and eccentricity of the nucleolus. The affected cells are frequently surrounded by an increased number of satellites (oligodendroglia nuclei).

It is suggested that the cellular changes of the cortical ribbon are secondary to the swelling of the underlying white matter and may readily be interpreted as the result of pressure and ischemia.

Widening of the pericellular and perivascular spaces of the gray matter, described by many observers as characteristic for cerebral edema, is too frequently seen as the result of formalin fixation or of embedding in paraffin to be considered as a reliable sign. Such changes are to be evaluated only in association with other, more reliable signs, such as vascular alterations, swelling of the nerve fibers and glia changes.

The accumulation of fluid, however, in the distended subpial space, as illustrated in figure 10, may constitute a fairly reliable sign of edema; it cannot be interpreted as an artifact resulting from poor fixation or embedding, because it is seldom observed under those conditions.

HISTORY

The term cerebral edema is one of long usage. Local edema of the brain has long been recognized as occurring in the vicinity of cerebral neoplasms and abscesses. Diffuse cerebral edema, on the other hand, has been reported in such diverse conditions as cerebral vascular accidents, uremia, severe intoxications and in status epilepticus.

Anton[2] defined cerebral edema as an increase in volume of the brain secondary to an increase of fluid in the perivascular and pericellular spaces. Reichardt[3] was the first to introduce the concept of cerebral swelling ("Hirnschwellung") as a specific reaction of nerve tissue. He defined it as an increase in brain volume, not due to hyperemia or to excess of free fluid. According to Reichardt, the brain is considered swollen when the difference between brain volume and skull capacity is less than 8 per cent. (The normal correlation between brain volume and skull capacity was first established by Rieger in 1885). Reichardt differentiated the following two etiologic groups of cerebral swelling: (1) cases in which the reaction was brought about by an exogenous agent (e. g., cerebral tumors, infections and intoxications); and (2) cases in which no exogenous cause can be discovered, as in epilepsy and catatonia. He believed brain swelling to be due to an alteration in the colloidal chemistry of the brain tissue unaccompanied by histologic change.

The relation between brain tumor and cerebral swelling and edema has been subject of many papers.[4–8]. Spatz came to the conclusion that true swelling of the brain is of common occurrence in cases of cerebral neoplasm, and is the direct cause of increased intracranial pressure. He also expressed the opinion that a distinction should be drawn between cerebral swelling and cerebral edema. It must be noted that in English and American literature the concept of cerebral swelling, as distinct from cerebral edema, does not exist; in fact, cerebral edema is the only term in common use. In French articles the two terms appear to have

been employed indiscriminately, and LeBeau[9] was of the opinion that it was not possible to make a distinction between them. His conclusions, however, were based entirely upon a gross study of the brain.

Until recently, cerebral swelling was considered as a pathologic reaction of the brain without any evident histologic changes.

In a series of cases of cerebral swelling the only abnormal findings noted by Wohlwill[10] was the presence of Alzheimer's ameboid glial cells. Spatz too, was unable to find any definite histologic alterations characteristic of brain swelling.[5] Only in some of his cases did he observe swelling of the processes of the astrocytes in the white matter and signs of clasmatodendrosis. In a clinical review of the subject, Pette[11] stated that, to date, investigations into the problem of the histopatholgy of cerebral swelling had proved unsuccessful.

The first attempt to outline the characteristic histopathologic features of brain swelling was made in 1938[12]. In subsequent papers it was emphasized that, despite the histologic difference between cerebral swelling and cerebral edema, the two conditions are actually two stages of the same biologic process.[1,13] Both pathologic conditions include morphologic signs of vascular alterations with increase in permeability of the vessel walls. It was concluded that circulatory disturbances are essential to the pathogenesis of both cerebral swelling and edema.

In cases of cerebral edema associated with brain tumors, Greenfield described degeneration of myelin sheaths and varicosities of axis-cylinders, swelling of astrocytes and slight proliferation of michoglia[14]. Kernohan came to the conclusion that increased intracranial pressure is the direct result of edema which, in cases of brain tumor, may either remain local or be generalized throughout the whole brain[15]. He accepted the view that edema is caused by circulatory disturbances resulting in hypoxia and acidosis of the brain tissue.

Histologic study has been supplemented by relatively few physiochemical and experimental investigations. In 1938 de Crinis showed that a considerable retention of urea in the brain tissue occurs in cases of cerebral swelling.[16] These findings were confirmed experimentally by Heim[17], who showed that retention of urea leads to increased absorption of fluid into the pericellular colloidal envelope. Both de Crinis and Heim expressed the belief that retention of urea, with consequent hydration of the albumin, is the fundamental cause of cerebral swelling.

The relationship between the wet and dry weight of the brain tissue was studied by Alexander and Looney[18]. They concluded that edema is confined almost entirely to the white matter of the brain. The gray matter of edematous brains disclosed the normal ratio between wet and dry weight.

Very significant contributions to improved understanding of both the histopathology and the physiology of cerebral edema are the experimental studies by White, Brooks, Goldtwart and Adams[19] and the recently reported study made by Prados, Strowger and Feindel[20].

CLINICAL CONSIDERATIONS

In a recent study it was demonstrated that swelling of one of the hemispheres is responsible for a syndrome described as "transtentorial brain stem herniation." [21] The same study brought out that herniation of a relatively small portion of compressible tissue (hippocampal herniation) is not the real cause of the gravity of the clinical syndome.

A histopathologic analysis of 55 cases revealed that most of the clinical symptoms and the frequent sudden deaths are to be ascribed to a frank herni-

ation of the rostral portion of the brain stem into the tentorial opening, followed by edema and hemorrhages within the vitally important midbrain centers. The syndrome previously designated by several investigators as "hippocampal herniation" or "temporal pressure cone" was described as "transtentorial herniation of the brain stem."

Of the numerous points that emerged from the study of transtentorial herniation of the brain stem, the following are briefly summarized:

Unilateral cerebral swelling as a frequent cause of brain stem herniation through the tentorial opening. In all cases of brain stem herniation associated with cerebral trauma, brain tumor, brain abscess or massive intracerebral hemorrhage, there is pronounced unilateral swelling of the affected hemisphere with shift and compression of the ventricular system toward the opposite side. The shift and compression the the ventricles is readily explained by the unilateral swelling of the brain, in some instances sufficient to cause displacement of the affected hemisphere across the midline under the free edge of the rigid falx.

In all cases under study, there was a herniation of the rostral portion of the midbrain through the tentorial opening. The homolateral side of the brain stem was considerably swollen. The aqueduct of Sylvius appeared displaced and compressed.

It is evident that, as a result of the swelling of the entire hemisphere, including the temporal lobe, the mesial portion of the latter lying immediately above the tentorial ring is the first to be displaced downward through the tentorial opening. With increased duration and severity of the brain swelling, a downward displacement and frank herniation, together with distortion and compression, of the midbrain take place.

Pathologic lesions produced by the transtentorial brain stem herniation.—On gross examination the midbrain appears swollen, as a rule, and reveals large numbers of small, coalescent hemorrhagic effusions (figure 7). No part of the brain stem appears immune from hemorrhage, though most of the hemorrhages are observed in the rostral portion of the brain stem and only relatively few are detected in the caudal portion. The great majority of hemorrhagic lesions are situated in the tegmental portion of the midbrain, chiefly in the periaqueductal region and in the median raphe. However, it should be emphasized that the brain stem lesions may occasionally be of such minimal degree that they may be easily overlooked on gross examination. Almost all cases of brain stem herniation disclosed, on microscopic examination, various stages of swelling and far advanced degenerative neuronal changes.

Origin and pathogenesis of hemorrhages of the brain stem.—In published reports on midbrain hemorrhages, stress has always been placed upon their arterial origin.[22] However, recently there has been brought forth evidence that hemorrhages of the brain stem are, irrespective of their etiology (cerebral

trauma, brain tumor, brain abscess or intracerebral massive hemorrhage), venous in origin and related to medium-sized and small veins. Often the hemorrhages may occur in the form of narrow bands, enclosing the extremely congested veins like a sleeve, either occupying the perivascular spaces or lying free in the adjacent nerve tissue. In many instances the small perivenous hemorrhages tend to fuse, thus giving rise to larger hemorrhages. Only in relatively few instances, when the hemorrhagic lesions are more extensive, may it be difficult or impossible to be sure of the source of the hemorrhage; this is mainly because of complete disintegration of the tissue and abundance of blood. Within the great majority of the smaller hemorrhagic lesions, however, there may be seen one or several tremendously congested veins with walls displaying advanced disorganization, but not real rupture. In some instances the veins are represented by mere outlines of their walls. These have undergone almost complete degeneration and the content of the veins merges with the extravasated blood surrounding the blood vessels. The perivascular spaces, maximally distended as a rule, are filled with large masses of serous fluid and red blood cells.

Swelling of the herniated brain stem.—In many of those cases in which the gross appearance of the herniated brain stem is normal or shows a moderate degree of increase in bulk, the microscopic examination discloses findings characteristic of tumefaction, edema or liquefaction. These changes are usually associated with congestion of the smaller veins and capillaries. Only occasionally are there small petechial hemorrhages within the distended perivascular spaces of some of the congested veins.

Pathophysiologic mechanism responsible for herniation and hemorrhages of the brain stem.—The following theory of the mechanism responsible for the development of edema and hemorrhage in the brain stem is proposed for consideration: Evidence is afforded that a sudden increase in bulk of one of the cerebral hemispheres caused by swelling of the brain leads to an acute increase in the supratentorial pressure. In the earlier stages the affected cerebral hemisphere displaces cerebrospinal fluid from the subarachnoid space and from the cisterns. At a later stage the ever increasing demand for space leads to profound shifts of cerebral substance; the initial formation of a temporal pressure cone is followed by downward displacement and herniation of the brain stem with subsequent plugging of the tentorial hiatus, producing a bottleneck for both the subarachnoid and the ventricular fluid. At the same time, the shifting cerebral substance may compress or occlude the narrow aqueduct of Sylvius, and the intraventricular fluid becomes trapped in the lateral and third ventricles. This leads to a steadily progressing disparity between the intracranial pressure above and that below the tentorium. With the constant increase of the intraventricular pressure the herniated portion of the brain stem is pushed deeper into the tentorial opening. As it progresses, it leads to compression and stretching of the superficial blood vessels, especially

the veins, with considerable obstruction of the venous circulation and a resultant, severe degree of congestion and stasis. The thin-walled, smaller veins, composed of simple endothelial tubes, are most likely to be vulnerable to compression and to hypoxic degenerative changes in their walls resulting from stasis. Thus, in the earlier stages compression of thin-walled veins between the impinging uncus and the brain stem is believed to occur. In the later stages the possibility of interference with free venous outflow is even greater because the cerebral substance and the intervening veins are jammed against rigid dural reflections. This is believed to result in a severe degree of congestion and stasis, local venous hypoxia due to the stasis, and possibly degenerative changes in the walls of the veins. Finally, if complete block of cerebrospinal fluid occurs, resulting in increased supratentorial pressure with complete herniation of the brain stem, the smaller veins are ready to give way and numerous perivenous extravasations take place. The small veins of the periaqueductal region are evidently poorly supported by the loose tissue of the gray substance, as compared with those of the white matter; which theory may explain the predilection of the perivenous hemorrhages for this region. The fixation of a certain number of the larger superficial veins of the brain stem for a long distance parallel to a bony surface makes them more exposed to the increased pressure.

The anatomic observations in support of this theory of mechanism may be listed as follows: (1) the gross and histopathologic evidence of swelling or edema of the brain present in the affected hemisphere; (2) transtentorial herniation of the rostral portion of the brain stem; and, finally (3) the predominantly perivenous character of the hemorrhages in the midbrain associated with far advanced venous congestion and stasis.

Experimental observations.—The relations between the ventricular and lumbar cerebrospinal fluid pressures has been studied experimentally by Kahn.[23] An extreme degree of edema of the brain was produced by the perfusion of distilled water in the common carotid artery of animals. During the experiments the cisternal and intraventricular pressures were recorded simultaneously.

A high intraventricular and relatively low cisternal pressure were constantly observed. The disparity was interpreted as probably due to herniation of the brain stem into the foramen magnum or through the incisure tentorii, with the creation of a resulting partial block between the lateral ventricles and the cisterna magna. The circulatory and respiratory embarrassment associated with high levels of intraventricular pressure could be relieved by ventricular drainage. No circulatory or respiratory embarrassment occurred when both the cisternal and the intraventricular pressures were at high levels; medullary embarrassment appeared soon after the cisternal pressure was lowered, the intraventricular pressure alone remaining high.

Clinical conclusions.—What additional therapeutic conclusions are to be

derived from the pathologic observations described? The following significant clinical points should be stressed:

Transtentorial herniation of the brain stem presents a grave hazard for the clinician and the neurosurgeon. It is evident that lumbar puncture and pneumoencephalography must be interdicted if the existence of the herniation of the brain stem has been clinically recognized or suspected.

Transtentorial herniation of the brain stem explains in some instances the fact that lumbar pressures are not always a true index of intraventricular pressures.

Patients with lesions of the temporal lobe appear to be graver clinical risks, probably because of the possible tendency toward development of transtentorial herniation of the brain stem. Therefore such manipulative procedures as lumbar puncture or pneumoencephalography are attended by greater risks.

It has been assumed in cases of supratentorial tumor in which death followed lumbar puncture that cerebellar herniation into the foramen magnum was responsible. However, it has not been explained how the intraventricular pressure could be transmitted to the posterior fossa. There is little doubt that transtentorial herniation of the brain stem is the important factor. The frequent absence of cerebellar pressure cone corroborates these conclusions.

Clinical and pathophysiologic evidence has been accumulated to prove that the hypothalamic nuclei contain the higher regulatory centers for respiratory and cardiac control. It appears that transtentorial herniation of the brain stem might result in an interruption of the cardiorespiratory pathways between the diencephalic and the medullary centers, and might be responsible for the irregularities in respiration and pulse, hyperthermia and sudden cessation of respiration, with a rapid, bounding and often irregular pulse.

Attempts to release the temporal pressure cone by removal of the herniated portion of the gyrus hippocampus has been suggested by Jefferson. The observations presented in this study suggest that section of the free edge of the rigid tentorium should be undertaken in an effort to distribute pressure more evenly. In many cases, particularly of tumor of the temporal lobe, this is technically possible.

It is conceivable that in certain cases the establishment of ventricular drainage might prove to be a life-saving measure, pending a more definitive operative attack.

SUMMARY

"Cerebral swelling" is the term proposed to denote the gross appearance of a brain characterized by a local or diffuse increase in bulk of one or both hemispheres.

The condition referred to grossly as cerebral swelling is represented microscopically by three types of histopathologic change, described as tumefaction, edema and liquefaction. The characteristic histologic criteria for recognition of, and differentiation among, the three types of lesions are given in detail.

Despite discrepancies in their histopathologic features, it is assumed that fundamentally the three conditions represent different stages of the same biologic process; occasionally they may merge insensibly one with another.

Attention is drawn to the significance of unilateral cerebral swelling in the production of transtentorial brain stem herniation.

The role of cerebral swelling in the production of midbrain hemorrhages is emphasized. These are believed to be perivenous in origin, and to be caused by an extreme degree of venous congestion resulting from compression and strangulation of the veins of the herniated midbrain.

In view of the gravity of the clinical symptoms resulting from transtentorial herniation of the brain stem, an attempt to distribute pressure more evenly by means of the establishment of ventricular drainage or by means of section of the free edge of the rigid tentorium may be a life-saving measure, pending final and more radical treatment.

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Extinction of Taste Sensation on Double Simultaneous Stimulation

Morris B. Bender, M.D. and Daniel S. Feldman, M.D.

THERE have been but few clinical studies of the sense of taste. Börnstein reported three cases of traumatic lesions of the parietal lobe[1] in which there was a sensory deficit for touch and pain as well as taste and lingual mobility on the side contralateral to the lesion. He concluded that the cortical representation of taste sensation was most probably in the vicinity of the parietal operculum contralaterally and that taste is more closely related to the somatic sensations of the mouth and tongue than to olfaction.

Blum and his co-workers[2] made electrolytic thalamic lesions in macaques in the vicinity of the arcuate nucleus and succeeded in raising the taste threshold to quinine but were unable to demonstrate in their animals associated somatic sensory deficits. There is very little else in the literature on taste. This may be due to the fact that routine examinations rarely disclose a distinct loss of taste in patients with hemiplegia and it has been assumed that there is no disorder in this modality. The literature has been reviewed extensively by Patton.[3]

Since previous experiences with the method of double simultaneous stimulation have demonstrated sensory defects which routine single stimulation failed to show, the sense of taste was investigated with this method. As a result several cases were found in which loss of taste could be shown on bilateral stimulation but not on single stimulation of the tongue. Twelve cases were examined. The etiology was varied. In most instances the cerebral lesion was acute but there were some in whom the defect in the brain was longstanding, e. g. cases of cerebral trauma sustained in World War II. Extinction of taste sensation was observed in three patients with gunshot wounds implicating the parietal lobe.

The following is a detailed report of one of the patients who had a right parieto-occipital lobe tumor. In this patient the sense of taste on the left side of the tongue was altered, but only under conditions of double simultaneous stimulation.

From the neurologic service, The Mount Sinai Hospital, New York City, and the department of neurology and psychiatry, New York University College of Medicine.

TABLE 1

DOUBLE SIMULTANEOUS STIMULATION WITH TASTE ON THE TWO SIDES OF THE TONGUE

Stimulus		*Perception*	
Right 1	*Left* 2	*Right* 3	*Left* 4
Sweet	sweet	sweet	sweet
Sweet	salt	sour	none
Sweet	sour	sour	none
Sweet	bitter	bitter	none
Salt	sweet	sour	none
Salt	salt	salt	none
Salt	sour	salt	none
Salt	bitter	salt	none
Sour	sweet	sour	none
Sour	salt	sour	sour
Sour	sour	bitter	none
Sour	bitter	sour	sour
Bitter	sweet	bitter	none
Bitter	salt	bitter	bitter
Bitter	sour	bitter	none
Bitter	bitter	bitter	none

For these experiments the 0.5 per cent concentration of quinine hydrochloride was used when bitter was tested.

The stimulus for the right and left side of the tongue on each trial is given in columns 1 and 2. The perception reported by the patient for the right and left side of the tongue is given in columns 3 and 4. Method of stimulation and reporting are given in the text.

CASE REPORT

R. O., a 65 year old man, was admitted to the Mount Sinai Hospital on December 29, 1950 with a three week history of left-sided weakness. At the onset of his illness there was difficulty with the use of his left hand, i. e. objects seemed to "turn outward" in the hand when he attempted to hold them.

1. Neurologic examination on admission: The patient veered to the left on walking. There was downward and outward drift of the outstretched left upper extremity and a dystaxia of the left sided extremities. There was a left faciobrachial paresis. There was a left homonymous hemianopic field defect. The deep tendon reflexes were generally depressed, particularly the left biceps. Position and stereognostic sensation were impaired on the left. There were no other sensory abnormalities under the conventional method of single stimulation. With double simultaneous stimulation, however, there was defective pain sensation in the left upper extremity.

A roentgenogram of the skull showed a slight displacement of the calcified pineal body to the left. An electroencephalogram disclosed a large parietotemporal slow wave focus on the right. A lumbar puncture showed no increase in the cerebrospinal fluid pressure and the spinal fluid contained total protein of 73 mg. per cent.

2. Course in hospital: Under observation there developed headache and by the ninth hospital day the left hemiparesis had become more pronounced. A left Babinski sign was present and a left-sided hemisensory defect to touch, sparing the face, became much more apparent on double simultaneous stimulation. On the thirteenth hospital day a right percutaneous arteriogram was done and a large parieto-occipital lesion was outlined. Herniation beneath the falx was pronounced. On the seventeenth day examinations of the sense of taste were first begun. It was then noted that taste sensation was extinguished on the

left side of the tongue on double simultaneous stimulation. Further studies were carried out and are described below.

3. *Methods of examination of taste sensation*: Taste was investigated using solutions designed to cause salt, sour, sweet and bitter perceptions. The salt solution contained about 10 per cent sodium chloride (W/V), the sweet, 30 per cent cane sugar, and the sour was a very dilute hydrochloric acid solution. A solution of quinine hydrochloride, approximately 0.5 per cent, provided the bitter solution. Serial dilutions of this solution were used to determine the taste threshold.

The test solutions were applied to the lateral margins of the protruded tongue by means of a cotton applicator. The patient was asked to raise his arm if he tasted anything. Immediately following the tasting he was given tap water with which to rinse his mouth. After the rinse he was asked to report the nature and location of the sensation. All tests were carried out with the patient blindfolded and random applications of tap water were tried, as well as dry stimuli, in order to check the accuracy of the reporting. Bitter stimuli were not tried until after the others had been used so that the problem of bitter after-sensation could be avoided. Single and double simultaneous stimuli were given.

4. *Tests with taste*: The results obtained with single stimulation showed that salt, sweet, sour and bitter solutions were correctly reported when applied singly either to the right or left border of the tongue. The site of stimulation was also localized without error. There was no difference in the threshold to quinine on either side nor on redetermination of the threshold at the end of the test period. The patient had a threshold of 0.1 per cent quinine hydrochloride. This was the same as in four normal controls. The results obtained with double simultaneous stimulation of taste sensation are summarized in table 1.

When taste stimuli were applied simultaneously to both sides of the tongue, on most trials the patient perceived no stimulus on the left. In several of the stimulations, however, the right sided stimulus was displaced to the left. At times the left sided stimulus was

TABLE 2

DOUBLE SIMULTANEOUS STIMULATION WITH SOMESTHETIC STIMULI TO THE FACE AND TONGUE

PART A				PART B			
Stimulus		*Perception*		*Stimulus*		*Perception*	
Right Tongue	*Left Tongue*	*Right Tongue*	*Left Tongue*	*Right Face*	*Left Tongue*	*Right Face*	*Left Tongue*
Pin	Pin	Pin	None	Pin	Pin	Pin	None
Pin	Touch	Pin	None	Pin	Touch	Pin	None
Touch	Pin	Touch	None	Touch	Pin	Touch	None
Touch	Touch	Touch	None	Touch	Touch	Touch	None

PART C			
Stimulus		*Perception*	
Right Tongue	*Left Face*	*Right Tongue*	*Left Face*
Pin	Pin	Pin	None
Pin	Touch	Pin	None
Touch	Pin	Touch	None
Touch	Touch	Touch	None

Part A: Stimuli applied to both sides of the tongue.
Part B: Stimuli applied to the normal cheek (right) and abnormal side of the tongue (left).
Part C: Stimuli applied to the normal side of the tongue (right) and abnormal side of the face (left).

displaced to the right, i. e. the patient indicated he perceived sour on the right side of the tongue, when a sweet stimulus was applied on that side in conjunction with a sour or bitter one on the left.

5. Taste and somesthetic sensation of the tongue: The somesthetic sensations of the tongue were also tested singly and in relation to simultaneous tests of somesthetic and taste sensation. These stimuli were also applied on both sides of the protruded tongue. There was no hypesthesia or hypalgesia with single stimuli applied to either side of the tongue. The patient was able to detect and localize the type of stimulus and to determine whether it was stationary or moving, wet or dry. On double simultaneous stimulation, stimuli applied to each side of the tongue, the sensation on the left was extinguished no matter what stimulus was applied (table 2). Also when the right sided stimulus was applied to the face there was no perception of the simultaneous stimulus on the left side of the tongue (touch or pin prick). Tactile and painful stimuli applied to the right side of the tongue similarly extinguished stimuli on the left side of the face.

TABLE 3

EFFECT OF SOMESTHETIC STIMULI ON THE NORMAL SIDE (RIGHT) ON THE SIMULTANEOUS PERCEPTION OF TASTE ON THE ABNORMAL (LEFT) SIDE

In Part A the protocol of experiments in which only the tongue was stimulated is given. Column 1 gives the stimulus applied to the right side of the tongue; Column 2 that to the left. Columns 3 and 4 list the responses as reported by the patient.

PART A

Stimulus		*Perception*	
Right 1	*Left* 2	*Right* 3	*Left* 4
Touch	bitter	bitter	bitter
Touch	sour	sour	sour
Touch	sweet	salt-sour	salt-sour
Touch	salt	salt	salt
Pin	bitter	pin	no sensation
Pin	sour	pin	pin
Pin	sweet	pin	no sensation
Pin	salt	pin	no sensation

In Part B the protocol of experiments in which the somesthetic stimulus on the "normal" (right) side was given to the face is presented. Columns 1 and 3 give the stimulus and perception on the right cheek (face) and columns 2 and 4 the stimulus and perception on the left side of the tongue.

PART B

Stimulus		*Perception*	
Right Face 1	*Left Tongue* 2	*Right Face* 3	*Left Tongue* 4
Touch	Bitter	Touch	Bitter
Touch	Sour	Touch	Sour
Touch	Sweet	Touch	Salt
Touch	Salt	Touch	Salt
Pin	Bitter	Pin	Bitter
Pin	Sour	Pin	Sour
Pin	Sweet	Pin	Sour
Pin	Salt	Pin	Salt

When touch or pin prick was given simultaneously with a taste stimulus the response was variable. At times there was displacement of the taste stimulus from the left to the right, at times complete extinction of the left sided taste stimulus, and on other occasions a displacement of the somatic sensation from left to right. All of these observations were made with the taste stimulus applied to the left side of the tongue (table 3A). Taste stimuli to the right side of the tongue with somatic stimulation on the left produced extinction of the left sided touch but not of pin prick only when bitter and sour stimuli were used. The patient, however, did not report the sensation of taste on the right (table 4). Facial stimulation in conjunction with taste on either side did not give extinction or displacement of taste on the right. However, there was failure to perceive touch and pin prick on the left side of the face and tongue when bitter and sour stimuli were applied on the right side of the tongue (table 4).

6. Cutaneous and proprioceptive sensations: Cutaneous sensibility was also tested extensively. There was a subjective hypalgesia on the trunk and extremities on the left but

TABLE 4

EFFECT OF TASTE STIMULI ON THE NORMAL SIDE ON THE SIMULTANEOUS PERCEPTION OF SOMESTHETIC STIMULI ON THE ABNORMALLY INNERVATED SIDE OF THE TONGUE AND FACE

Part A of this table gives the results of stimulation of the tongue only. Columns 1 and 2 list the stimuli and 3 and 4 the perceptions as reported by the patient. "No taste" is the equivalent of a statement by the patient "I feel something but I don't taste anything." The location of the untasted stimulus was always correctly given.

PART A

Stimulus		*Perception*	
Right 1	*Left* 2	*Right* 3	*Left* 4
Bitter	Touch	No taste	No sensation
Bitter	Pin	No taste	Pin
Sour	Touch	Sour	No sensation
Sour	Pin	No taste	Pin
Sweet	Touch	No taste	Touch
Sweet	Pin	No taste	Pin
Salt	Touch	No taste	Touch
Salt	Pin	No taste	Pin

Part B gives the results of taste stimulation on the normal side given simultaneously with somesthetic stimuli on the abnormal (left) side of the face. Columns 1 and 3 give the stimulus and response on the right side of the tongue and columns 2 and 4 the same data with respect to the left cheek.

PART B

Stimulus		*Perception*	
Right Tongue 1	*Left Face* 2	*Right Tongue* 3	*Left Face* 4
Bitter	Touch	Bitter	No sensation
Bitter	Pin	No taste	No sensation
Sour	Touch	Sour	No sensation
Sour	Pin	Sour	No sensation

stimulation with a pin point was described as sharp and correctly localized. Single stimuli with light touch and a vibrating tuning fork were perceived normally on either side of the body. However, kinesthetic and position sensation, two-point discrimination and thermal sensitivity were impaired on the left.

Double simultaneous stimulation of homologous areas on the extremities with touch, rubbing or pin point often yielded extinction of the sensation evoked by the left sided stimulus, in the pattern which was described previously.[7] Displacement was also noted. Stimulation of both cheeks or both sides of the forehead resulted in correct perception and localization of both stimuli. However, when the forehead on one side and the cheek on the other were tested simultaneously the left sided stimulus was displaced and felt in the area homologous to that on the right side. For example: pin prick on the right cheek and touch on the left forehead were felt as pin prick in both cheeks. A left-sided vibration stimulus to the limbs was extinguished by simultaneous touch or pin prick on the right whether or not the contralateral stimulus was on a homologous or heterologous portion of the trunk or extremities.

7. *Auditory sensation*: When the patient was blindfolded he was able to lateralize the source of a tone from a vibrating tuning fork and to discriminate between two tuning forks an octave apart. Weber and Rinne tests were normal and clinically there was no hearing defect. There was extinction of hearing on the left on double simultaneous stimulation with tuning forks of the same and different pitch. The tuning fork applied to the right ear was always correctly identified for pitch. (Air conduction was used.)

8. *Visual sensation*: At the time of admission to the hospital a left homonymous hemianopic field defect was apparent but this was not definite unless the method of double simultaneous stimulation was used. With targets in the right and left half fields of vision he perceived the one on his right but not on his left. Under these conditions there was a left homonymous hemianopsia.

9. *Olfactory sensation*: There were no defects noted in olfaction in either nostril or when both were tested simultaneously.

10. Mental status: At the time of these examinations the patient was oriented for place and person but could only give the year. There was no right-left disorientation on his own body but identification of parts of the examiner's body was somewhat impaired. There was no evident disturbance in language function and no errors in naming were made. He was apathetic but he remained alert during the course of the examinations. Cooperation was fair; attention was somewhat variable in that the patient was distractable from the object of the tests, but it remained fairly good throughout the course of the test periods. These studies were done at four sessions.

Further course: By the nineteenth day the patient had become incontinent of urine and feces, somnolent, and difficult to arouse with either verbal or painful stimuli. From here on special sensory examinations could not be carried out. On the following day a craniotomy was done. A large cystic infiltrating tumor was uncovered in the right parieto-occipital area and a smaller abnormal area was seen at the junction of the temporal and occipital lobes. The larger tumor was partially resected and the smaller lesion biopsied. Pathologic examination showed the large area to be a "transitional glioma with spongioblastic orientation" (glioblastoma multiforme). While he withstood the operative procedure well and was more alert immediately postoperatively than prior to the procedure, he grew steadily worse and died two weeks after surgery. Permission for autopsy was not obtained.

DOUBLE SIMULTANEOUS STIMULATION OF TASTE IN THE NORMAL

One might ask what are the reactions to taste stimuli using the method of double simultaneous stimulation in normal subjects? For this reason taste was studied intensively in relation to perception of simultaneous touch and pain stimuli in many normal subjects. There was no extinction of taste when stimuli were applied simultaneously to either side of the tongue. However, these subjects were somewhat variable in reporting sour and salt stimuli applied both singly and in relation to other stimuli on the face and tongue applied simultaneously. Salt was reported as being salt or sour, and sour as sour or bitter. On double simultaneous stimulation of taste the only errors in reporting were made with the salt and sour solutions. Simultaneous stimulation of the face and tongue similarly failed to give either extinction or displacement.

DISCUSSION

Extinction of sensation on double simultaneous stimulation has been described for cutaneous, proprioceptive, visual and auditory stimuli. The present communication is a description of the phenomenon of extinction for taste. In some of the cases not only was there extinction of taste but of cutaneous, visual and auditory modalities. It should be borne in mind that there was no extinction when two different modalities were simultaneously tested. Thus, there was no extinction when cutaneous and visual, cutaneous and auditory, or auditory and visual pairs were examined. With few exceptions, extinction occurred only when two different regions of the sensory field of one modality were simultaneously stimulated. Thus, in tests of the cutaneous sensory field, there was extinction when two touch stimuli, touch and pin prick, vibratory and pin prick, or upon application of any combination of stimuli in which contact was made with the skin. The common denominator in all of these

conditions of testing is tactile stimulation in the cutaneous sensory field, whatever other sensation may be evoked, such as vibration, kinesthesis, temperature or pain. In the light of these observations it might be understood why contact with the tongue obliterated such a special sense as taste. Nevertheless it should be emphasized that the foregoing observations do not exclude intermodal types of extinction. These may be observed under certain conditions which have been discussed elsewhere.[4,5,6]

According to Patton and Ruch sensory complexes referred to as taste are inextricably co-mingled with somesthetic sensations.[7] Therefore, taste might be influenced by tactile or painful contact with the skin, just as the sense of vibration can be extinguished when there is a concomitant pin prick in another part of the body.

In the case described in detail the disturbance of taste perception was parallel to the disorder in perception of painful and touch stimuli on the left side of the body, face and tongue. Where the taste stimulus on the right side of the tongue succeeded in causing extinction of a dissimilar stimulus on the left side of the tongue or face it must be noted that when the right side of the tongue was tested for taste, there was also a touch stimulus.

In contrast to this case there were other cases where there was extinction for taste but the patients were often aware of the touch stimulus. On subsequent tests with single stimuli the subject perceived taste but often this ability to perceive taste did not return even after several seconds. Evidently a dissociation of the touch and taste sensation can occur.

It should be noted that not all patients with hemiplegia or hemisensory syndrome have a concomitant loss of taste even on using the method of double simultaneous stimulation. The exact incidence of defective taste sense under these conditions is not known. Moreover, we have no information as to what particular structure in the brain must be damaged to obtain this defect in taste. From the available data and from observations made by Börnstein,[1,8] one would conclude that the parietal lobe is one area which must be involved to produce reduction of taste.

In many instances there was a mislocalization of taste sensation. On simultaneous application of sour on one side and sweet stimuli on the other, the subject often displaced the stimulus on the affected half (side opposite to the cerebral lesion) to the normal side of the tongue. This, however, was not a consistent phenomenon. Moreover, this type of displacement of taste occurred in normal subjects. Therefore, no definite conclusions can be drawn as to displacement of taste sensation but the phenomenon of extinction for taste sensation can be regarded as consistent and real.

SUMMARY

Studies in taste sensation were made in patients with lesions of the brain. In a patient with a glioma in the right parieto-occipital region there was extinction of taste on the left side of the tongue when both sides of the

tongue were simultaneously stimulated. Taste threshold obtained with single stimulations was equal and apparently normal on the two sides of the protruded tongue. Alterations in cutaneous sensibility most marked on double simultaneous stimulation were also demonstrated. There was crossed extinction between simultaneous taste and cutaneous stimulation. The significance of these phenomena in relation to patterns of alteration of cutaneous sensibility are discussed.

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The course of nerve-fibres is often very different from that suggested by the course of the nerves in which they run, and the arrangement and connection of the elements of the brain is often not the same as that suggested by the coarse morphological relations of its parts. The course of the fibres of the cranial nerves affords many illustrations of these anomalies. A comparatively simple instance arises from the same gray matter as the cervical nerves, is distributed to the same muscles, but has a course that takes it just within the entrance to the cranial cavity, although it has no business there, as far as we can see, to justify its ascent. The course of the fibres that subserve taste is a more elaborate instance of the same thing, and it has caused difficulties from which neither anatomical nor physiological investigation has yet cleared our knowledge.

—Sir William Gowers, in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published 1885.

Subarachnoid Hemorrhage as a Cause of Sudden Death

Weir M. Tucker, M.D. and Bernard J. Alpers, M.D.

SUBARACHNOID HEMORRHAGE may, on rare occasions, be a cause of sudden death, without accompanying cerebral or ventricular hemorrhage. This fact, not generally recognized, serves to impress the seriousness of outlook in some cases of subarachnoid hemorrhage, and at the same time raises the question of the cause of death in fatal cases. It is for these reasons that two verified fatal cases of subarachnoid hemorrhage are reported.

REPORT OF CASES

Case 1.—Sudden death in 35 minutes following subarachnoid hemorrhage. No other cause of death determined. Herniation of medulla into foramen magnum and aneurysm (7 mm.) of anterior communicating artery.

History: A physician 54 years of age was apparently well until May 16, 1941, when he suddenly fell to the floor unconscious while straining at stool. In 35 minutes he was dead. For several years he had suffered from migraine headaches which had never resulted in permanent residuals of any type. Apart from the generous use of analgesics in order to control his attacks of headache, he had required no medical attention. Examination at the time of his collapse revealed an unconscious subject who died shortly after arrival of a physician.

Autopsy disclosed no evidence of coronary occlusion or pulmonary embolism. The brain was average in size, weighing 1510 Gm. It was somewhat soft and edematous, the gyri of both hemispheres appearing swollen, with the intervening sulci obliterated. The base of the brain was covered with an extensive fresh hemorrhage, but clotting had occurred in the cisternae and pontis. A thin film of hemorrhage covered the cerebral hemispheres incompletely. Coronal sections revealed extension of the hemorrhage into both Sylvian fissures. No hemorrhage was seen in the brain or brain stem, but there was a thin film of hemorrhage within the lateral ventricles. Dissection of the heavy subarachnoid hemorrhage over the base of the brain revealed a small aneurysm measuring 7 mm. in diameter, arising from the anterior communicating artery. A small aperture was found in the artery, quite obviously the source of the bleeding. At the base of the brain was a large foraminal herniation involving the medulla and cerebellar tonsils which had been forced into the foramen magnum.

Microscopic examination of the brain revealed extensive hemorrhage in the subarachnoid space over the base of the brain and less extensive hemorrhage over the cerebral cortex. The red cells were well preserved and there was no evidence of organization. No hemor-

From the department of neurology, Jefferson Medical College, Philadelphia, Pennsylvania.

rhage, punctate or massive, was found anywhere in the brain. The pia-arachnoid membranes were slightly fibrotic, consistent with the age of the patient, and some of the vessels in the pia showed signs of early arteriosclerotic changes. The cortical ganglion cells here and there were pale and shrunken, with prominent apical dendrites, and eccentric and pyknotic nuclei. The cortical arterioles were thickened.

Summary: This patient, a busy physician of 54 years, became unconscious while straining at stool and was dead in 35 minutes. Apart from a history of recurrent migraine, he had no known illnesses. Autopsy revealed an extensive subarachnoid hemorrhage at the base of the brain which became much thinner over the cerebral hemispheres. There were no gross hemorrhages within the brain substances, but a thin film was found in the lateral ventricles. A small aneurysm (7 mm.) was found on the anterior communicating artery and a well-pronounced foraminal herniation was present. No other cause of death was found. Coronary disease and pulmonary embolism were excluded as cause of death.

Case 2.—Migraine for many years. Evidence of cerebral aneurysm two weeks before admission. Subarachnoid hemorrhage and death in 25 minutes. Autopsy revealed subarachnoid hemorrhage and ruptured posterior communicating artery aneurysm.

History: A 58 year old white woman was admitted to the hospital on September 21, 1947. For many years she had suffered from headaches confined to the right side of the head, occurring at two to four week intervals, and associated with nausea and vomiting. These had been regarded as typical migraine headaches, and indeed appeared to have all the features of such headaches. Two weeks before admission to the hospital she developed sudden persistent pain behind the right eyeball. She had no other symptoms save the right retro-orbital pain which defied relief. One week after its appearance, during a trying telephone conversation in her capacity as secretary to a physician, she suddenly experienced a bursting sensation in her head. The headache was intense and was followed by slight drooping of the right eyelid and diplopia. With the persistent and constant headache there developed in the course of 24 hours a complete ptosis of the right eyelid and an inability to rotate the eyeball, associated with diplopia. At this time she entered the hospital for study.

Neurologic examination revealed unequal pupils, the right being larger, the right pupil reacting slightly to light and consensually, and the left promptly; a ptosis of the right eyelid; loss of upward and downward movement of the right eyeball and impairment of inward movement. All other findings were normal.

The temperature, pulse and respiration were normal. The blood pressure was 160/104 mm. Hg. Routine blood studies, the Wassermann and Kahn reactions of the blood, urea nitrogen and urea clearance were all normal. The urinalysis was normal. The spinal fluid was clear, with a pressure of 130 mm. of water, with a protein of 25 mg. per 100 cc., 3 cells, and a negative Wassermann reaction and colloidal gold curve. The electrocardiogram revealed a mild left axis deviation. Roentgenograms of the skull were negative.

The patient endured increasingly severe pain in and about the right eye with straining. On her third hospital day she gave a sudden cry at 9:15 a.m., fell back on the bed, had a generalized convulsion, and became unconscious. She died at 9:40 a.m., presumably of a ruptured aneurysm with subarachnoid hemorrhage.

Autopsy revealed no evidence of coronary occlusion or pulmonary embolism. A fresh and thick hemorrhage covered the entire base of the brain, extending into the Sylvian fissures, but did not penetrate into the subarachnoid space over the cerebral hemispheres. A small ruptured aneurysm was found on the right posterior communicating artery. Coronal sections revealed extensive subarachnoid hemorrhage over the entire brain stem, but no punctate or massive hemorrhage was seen in the brain tissue except for a tinge of blood in the lateral ventricles. The blood vessels were normal in appearance except for the aneurysms mentioned.

Microscopic examination revealed fresh blood in the subarachnoid space over the base of the brain. No punctate or other gross hemorrhage was seen. There was no evidence of organization of the hemorrhage. The ganglion cells were well preserved and were normal in structure. The blood vessels, both intrinsic and extrinsic, revealed no evidence of disease.

Summary: This patient, a 58 year old woman, suffered from typical migraine headaches for many years, followed two weeks before admission by evidence of development of signs of a cerebral aneurysm without subarachnoid bleeding. During the course of her hospital stay she suddenly complained of intense headache, developed a generalized convulsion, and in 25 minutes was dead. Autopsy revealed extensive subarachnoid hemorrhage over the base of the brain due to a ruptured right posterior communicating artery aneurysm. There were no gross hemorrhages anywhere in the brain. No foraminal herniation was disclosed.

DISCUSSION

Subarachnoid hemorrhage may be a cause of sudden death, but it is not a frequent cause of such death. Martland[1] states that 2 per cent of sudden death from natural causes result from spontaneous subarachnoid hemorrhage. He estimated that one half of the fatal cases of spontaneous subarachnoid hemorrhage died within one hour of rupture, while the rest lived only a few hours or days. Ayer[2] states that subarachnoid hemorrhage occurs in 7 per cent and parenchymatous hemorrhage occurs in 8 per cent of all cerebrovascular diseases. Among 2030 autopsied cases of sudden death Helpern[3] found 95 cases or 4.7 per cent due to subarachnoid hemorrhage. Rapid death from rupture of a cerebral aneurysm into the subarachnoid space was recognized early.[4] Relatively few reports are available in the recent literature, however, and in almost no instance is the actual time intervening between onset and death given specifically. Courville[5] reports two cases of sudden death following rupture of the anterior cerebral artery. Two similar cases, one without disclosure of the source of the bleeding, are reported by Helpern,[3] and Moritz[6] also reports a similar case. In the two cases here reported death occurred in 35 and 25 minutes following the first symptoms of subarachnoid hemorrhage. No other instances have been found in a careful search of available reports. There are many instances of reports of sudden and unexpected death following subarachnoid bleeding, but these have been discarded if no time relationships were recorded, or if death did not occur in less than one hour.

The course of sudden death in subarachnoid hemorrhage is not clear. In case 1 here recorded, an extensive foraminal herniation explained the sudden death satisfactorily as a consequence of respiratory paralysis. No such mechanism was found in case 2. Forminal herniation may account for some cases but it is not always found. The amount of bleeding and the associated brain edema do not in themselves appear to account for the sudden death since they occur with equal severity in cerebral and ventricular hemorrhage, neither of which is a cause of sudden death.[7–12] Death resulting from cerebral hemorrhage consumes hours and sometimes days, while death from ventricular hemorrhage is also a matter of hours. Jackson and Sanders[13] report that 65

per cent and Jones[14] 60 per cent of cases of ventricular hemorrhage die in the first 24 hours. In a clinicopathological study of 245 cases Aring and Merritt[15] report five cases with an interval of less than 12 hours but none with less than three hours. In a study of 205 cases Rose[16] concluded that in no instance did death take place in less than 2 hours, although 80 per cent died within 24 hours. On the other hand, Pieczarkowski[17] found in a study of 6,000 autopsies that 42 or 5.75 per cent were due to cerebral hemorrhage.

That sudden death may occur in subarachnoid hemorrhage due to a ruptured aneurysm seems quite evident from the cases here recorded as well as from the experience of others. Death in the instances related for review has occurred within an hour after the onset of symptoms and has simulated the sudden death occurring from cardiac disease. In none of the recorded cases has there been evidence of coronary disease or of pulmonary embolism. The mechanism of the sudden death occurring in subarachnoid hemorrhage is not entirely clear. In some instances sudden increase in intracranial pressure with foraminal herniation of the medulla seems to account for death, but in other instances no definitive cause can be assigned.

SUMMARY

1. Two verified cases of subarachnoid hemorrhage as a cause of sudden death are reported.

2. Extensive foraminal herniation explained the sudden death in one case.

3. Edema and severity of the hemorrhage were not primarily responsible.

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The Role of Neuroanatomy in Neurologic Research

Alf Brodal, M.D.

*An einer festgestellten anatomischen Tatsache ist nicht zu rütteln, gleichviel ob sie mit unseren Beobachtungen am Lebenden im Einklang oder im Widerspruch steht; ihrer Wucht haben sich Beobachtungen und Auffassungen zu beugen.**

W. VON SPIELMEYER

THIS FAITH in morphologic research was expressed some 25 years ago by Walther von Spielmeyer, one of the founders of modern neuropathology. His concise dictum may serve appropriately as a motto for a discussion of the role of neuroanatomy in contemporary neurologic research.

Today, as 25 years ago, we must admit that our knowledge of structure of the living organism frequently cannot be brought wholly into accordance with observations of its signs of function. Certainly this is true for the nervous system. Neurophysiologists have often reported phenomena which from an anatomical point of view appear strange and which – if we presume that the functions of the nervous system are dependent on a morphologic substratum – cannot be made to agree with morphologic facts. Almost daily we see how morbid processes involving the nervous system do not produce those symptoms and signs which we would expect from our knowledge of its structure. In this situation, we may appropriately pose the question whether Spielmeyer's words are still valid, and more particularly whether they hold true with regard to the nervous system. If we are to decide this, it is necessary first to make clear the tasks of neuroanatomy of today, and then to consider whether means and possibilities are at its disposal to solve these tasks. Only when these questions have been answered may the relation of neuroanatomy to other branches of neurologic research be considered. From the outcome of this discussion it may be possible to express an opinion on the truth of Spielmeyer's credo in our time.

Let us first make clear the meaning of the expressions "neuroanatomy" and "neurologic research." In a rather broad sense, "neuroanatomy" will be taken to include all those aspects of the study of the nervous system which

*An established anatomical fact is not to be shaken, regardless of whether it is in agreement with or contradicts our observations in the living; to its weight observations and opinions have to yield.

From the Anatomical Institute, University of Oslo, Norway.

are directed at unravelling its normal structure: the charting and delimitation of groups and aggregations of nerve cells; the tracing of mutual interconnections between cell groups and nuclei; the study of the morphology of individual nerve cells; the occurrence and spatial distribution of cells of different types; quantitative aspects of nerve cells and fibers; comparative investigations of the nervous system in various animal species; studies on the ontogenetical development of the nervous system; studies on its blood supply and its supporting elements. It goes without saying that the borders between neuroanatomy and neuropathology are indistinct.

The concept "neurologic research" will be taken to embrace all those lines of research which have as their subject the study of the nervous system. Therefore, in addition to neuroanatomy it includes experimental animal physiology of the nervous system; experimental studies of the nervous system in man; clinical research in neurology, with its diagnostic and therapeutic, including surgical, problems; neuropathology; psychiatry and psychology and the study of the physicochemical constitution of nerve cells and their life processes.

The history of neuroanatomy, fascinating though it is, is far too comprehensive for review here. Suffice it to mention that Hippocrates and Galen already knew some gross features of the morphology of the nervous system, and that the greater part of those structures which are visible to the naked eye were described in the years from about 1500 to 1800. Such names as Varolius, Willis, Pacchioni, Monro, Vicq d'Azyr, Rolando, Soemmering and many others are inseparably linked with certain anatomical formations and remind us of these founders of neuroanatomy. Yet the real expansion of this branch of science did not begin until 60 or 70 years ago, when rapid advances in microscopic technique and the development of special staining methods for nervous tissue made it possible. Much has been elucidated since then in diligent studies by research workers from many countries.

Among men of the medical profession the view seems to be prevalent that although our knowledge of the functions of the nervous system is still fragmentary, its structure is quite well known. Any textbook of neuroanatomy is apt to strengthen this opinion in those not especially acquainted with the nervous system. Have not its various parts been described in far more detail than can possibly be of importance? What do we need to know, for instance, of the structure of the superior colliculus in addition to the meticulous account of its layers, with their different composition and orientation of cells and fibers, found in these textbooks? Are we not sufficiently informed of those fiber connections of the nervous system which may be imagined to be of functional importance? And is there anything to add to Campbell's, Brodmann's and v. Economo's detailed parcellation of the cerebral cortex into 50 or more small areas, differing with regard to their cellular architecture?

Indeed, the wealth of available information on the structure of the nervous system seems overwhelming, and there are many who consider all these ana-

tomical minutiae as superfluous ballast, particularly perhaps research workers who are inclined to emphasize the mass function of the cerebral cortex and are adherents of the views set forth by Goldstein, Lashley and others.

Alas, the tremendous expansion of neurophysiology in the last two decades has made it painfully clear to anatomists that in spite of considerable knowledge of the morphology of the nervous system, our information of this subject is extremely inadequate. The refined techniques which enable the neurophysiologist to stimulate minute parts of the nervous system and to register electrical alterations from a few, in some cases even single, nerve fibers, have raised questions for which the anatomist is not able to provide adequate answers. The neuroanatomist of today is in a deplorable dilemma: He is convinced that the phenomena which his physiologic colleague observes are dependent on and conditioned by a morphologic substratum, but too often he is quite at a loss when asked to point out the relevant substratum. We have every reason to believe that the numerous nervous impulses which at any time traverse the nervous system do so along definite bundles of nerve fibers, and that consequently the pathways of the nervous impulses are determined by the anatomical arrangement of these fiber systems. Even if evidence is accumulating that, in addition to this passage along structurally defined pathways an effect of electrical fields outside the conductor proper has to be considered, this does not reduce the need for a detailed knowledge of the structural features, but rather tends to emphasize the necessity of a complete mapping of the conducting elements.

Recent neurophysiologic discoveries have thus brought into the focus of interest the smallest units within the nervous system, the single nerve cells. Questions regarding their exact location and their mutual arrangement within the enormous numbers of neuronal chains making up the nervous system have become of imperative importance. For the anatomist of today to be able to express an opinion on the findings of the physiologist and to point out the morphologic substratum of the registered phenomena, he will, therefore, have to know the smallest details of the structural organization of the nervous system. He can no longer be content with knowing the connections between different parts in their principal features only; he is obliged to know their minutest particulars, their patterns of organization. Another aspect of relevance is presented by the numerical proportions of cells and fibers. Following the discovery of functional differences among axons of different caliber as, for instance, the greater conduction velocity in coarse fibers as compared with thinner fibers, the thickness of the nerve fibers is a feature of importance and must be taken into consideration. Last, but not least, the problem of how the different nerve cells establish contact with each other will frequently be decisive. We have recognized for some time that the morphology of synapses varies considerably, but we are still far from knowing these complicated features in sufficient detail and from knowing their variations in different parts of the nervous system.

The time appears ripe to ask: Does neuroanatomy have any possibility of clarifying these details, of unravelling the enormous wealth of structural minutiae which we would like to know? The answer to this question will decide the continued raison d' être of neuroanatomy.

When we raise the question whether neuroanatomy has possiblities to solve the tasks thus set for it, the problem of its methods is a fundamental one. It is becoming increasingly evident that in neuroanatomical research today the most valuable results and the most complete information are to be expected from experimental studies on animals. When it is possible to destroy at any place as small a part of the nervous system as is judged feasible and to study the ensuing degeneration of nerve cells and fibers after an appropriate lapse of time, then opportunity is afforded for the performance of systematic studies. Experimental investigations of this kind, although already employed by pioneers like Gudden, von Monakow, Ferrier and others, have played a role of steadily growing importance in neuroanatomical research.

In 1892 Nissl discovered that, following transection of a neurite, in the course of a few days its parent cell undergoes typical structural changes called by Nissl "primäre Reizung," and Marchi about the same time announced his osmium-method of impregnating myelin sheaths of degenerating nerve fibers. Both these methods have been extensively employed in neuroanatomy ever since. But Marchi's method, valuable as it is, has its definite limitations. It does not permit the tracing of fibers devoid of a myelin sheath, quantitatively by far outnumbering the myelinated ones, and the actual termination of the nerve fibers lacking myelin cannot be determined. Nissl's method, likewise, has its limitations. However, both methods are still among those which may be employed with success to solve certain problems. There is reason to believe that in many instances more precise information can be obtained by the use of very young, almost newborn animals, since the nerve cells react more rapidly shortly after birth and display more marked changes to a damage of their neurites than do cells in older animals. This modified Gudden method (Brodal 1940) has proved very useful in studies of some afferent cerebellar connections.

Among methods capable of disentangling the detailed organization of the nervous system, the socalled method of terminal degeneration has in recent years come into the foreground. This method is based on the affinity of degenerating axons and their terminal arborizations to silver salts, and several modifications are in use. Particularly where nerve fibers establish synaptic contact with perikarya or dendrites of other nerve cells by means of so called terminal boutons, this method permits an exact determination of the termination of transected neurites. The value of the method is evidenced by the results obtained in various studies.

There is reason to believe that this method of terminal degeneration will prove a most valuable tool in the clarification of details of nervous connections, and that its use will make possible the determination of a considerable

number of those finest particulars which are today urgently needed. Whether the intravital methylene blue method worked out by Feindel and his collaborators will contribute materially to the elucidation of central nervous connections remains to be seen, but for the study of the finest arborizations of peripheral nerve fibers this method appears to be the method of choice.

Even if the method of terminal degeneration appears to be particularly fruitful in the present state of neuroanatomical research, this does not mean that other methods can be dispensed with. In addition to and as a supplement to those already mentioned, careful analyses of cytoarchitecture, of the types of nerve cells and of their arrangement in different nuclei are still necessary. Are we not almost forced to conclude that, when the cells composing the various nuclei in the central nervous system differ morphologically and are arranged in definite patterns, this must be a reflection of different functional properties, even if we have to admit that we are as yet only vaguely able to surmise the importance of certain of these cytoarchitectonic differences, as for example of those occurring in the cerebral cortex. Yet, is it undue optimism to think that the day will come when we shall be able to interpret the finest morphologic peculiarities in the light of function? From this point of view the recently developed histochemical methods will also have to be employed in the study of the nervous system. Our knowledge of the complex metabolic processes incessantly going on in the nerve cells are still fragmentary, to say the least, but recent studies on the formation and chemical composition of the Nissl-substance, as well as histochemical studies on intracellular enzymes, seem to promise that here a fertile field of research is being opened. The recent discovery by Scharrer and Sinden of marked differences with regard to enzymes in the different layers of the optic tectum of birds is an indication of the value of such methods.

Many other well merited and well known methods will, however, still maintain their place in the neuroanatomist's armamentarium, even if they are not primarily directed at the study of the minutest structures. That comparative anatomical studies, particularly when embryonic stages are also evaluated, are still able to bring forth data of importance, is evidenced for instance by studies on the development of the cerebellum by Larsell and by Jansen. Comparative studies of the structure of certain nuclei in different animals are likewise of interest. Quite frequently such studies reveal considerable unsuspected species differences and serve as a reminder that the nervous system is far more complex and less uniform throughout the vertebrate scale than one would commonly believe. A relevant example is furnished by Walberg's studies of the lateral reticular nucleus of mammals. Embryologic studies elucidating how, when and from where the different parts of the central nervous system are derived may also shed light on important questions, especially when the experimental approach is employed. Harkmark's experimental demonstration of the cellular migration from the rhombic lip to form the inferior

olives and the pontine nuclei in the chicken serves to illustrate the point in question.

When the possibilities of studying the finest details of the nervous system are discussed, however, there is one old, well known method which more than any other deserves to be brought into the foreground. The Golgi method of 1873, which Fridtjof Nansen was one of the first to use in 1887 with great success, will experience a renaissance. It must be conceded that the Golgi method is cumbersome and capricious and this is probably the reason why it has been relatively little employed in recent years. It is, however, the only method available at present which permits the demonstration of single nerve cells with all their processes. Of particular importance is the fact that it makes possible a study of the course and arrangement of the dendrites. When findings made by Golgi's method can be supplemented by experimental studies of the terminal degeneration of afferent fibers to the region in question, significant details in the synaptic connections can be revealed, as shown recently by Blackstad in studies on the commissural connections of the entorhinal and adjacent cortical areas in the rat.

We may be justified in concluding that neuroanatomy today has at its disposal methods which enable us to clarify at least a considerable number of those structural details which are so urgently needed. Like all other biological methods, the anatomical ones are, of course, hampered by sources of error which must be known and taken into consideration. The greatest hindrance to a rapid progress in our knowledge of the structure of the nervous system is, however, not to be sought in methodical difficulties but in the lack of research workers endowed with the endurance and patience necessary to tackle research projects which do not immediately yield great and glorifying results.

These features of anatomical research in addition to the bustling tempo of our time are probably the causes of the fact that some neuroanatomists have in later years turned to neurophysiology where, owing to modern technical developments, rich and palatable fruits are still to be reaped. It seems, however, that we are now approaching with increasing speed the time when the full understanding of many new neurophysiological observations will be delayed by lack of knowledge of their morphologic substratum. We may indeed anticipate that this state of affairs will in turn have its repercussions on continued progress in neurophysiology. There is at present an urgent need for anatomical studies of the nervous system. If sufficient time and energy can be devoted to such studies, there is little doubt that neuroanatomy will be able to solve the problems with which it is faced.

With this in mind, let us now turn to the question of the role of neuroanatomy in other branches of neurologic research. In doing so we enter a wide field which invites and deserves discussion. It may be appropriate to direct attention to an elementary fact which concerns anatomy as such and consequently is also of relevance to neuroanatomy: It is almost a truism that

morphology has only limited value as a scientific discipline if its results are not evaluated in the light of function. It is equally clear, however, that studies of functions without due consideration of their organic basis remain incomplete and not fully intelligible. Knowledge of the structure of the nervous system, therefore, provides an absolutely necessary basis to all those branches which are concerned with nervous functions. Thus neuroanatomy will be of fundamental importance to experimental animal neurophysiology and to clinical neurology and psychiatry, as well as to its sister science neuropathology.

Let us first dwell on its role in experimental animal neurophysiology, which in the last two decades has amplified our understanding of the nervous system more than any other line of research. It will suffice here to mention some examples which serve to illustrate these relations and to set forth some general considerations.

The recent studies on the physiology of the spinal cord by Lloyd and others have made an exact knowledge of the synaptic connections within this, the simplest organized part of the nervous system, an urgent problem. Cajal's studies on normal material form a valuable basis, but many pressing problems still await experimental solution.

Recent neurophysiologic studies on the so-called rhinencephalon have made it clear that extensive parts of this have functions which can scarcely be called olfactory, an assumption which must be made also on the basis of a critical evaluation of available anatomical data. Much remains to be done on the anatomy of this part of the brain. Thus we are still almost completely ignorant of the pathways mediating the effects observed on stimulating the rhinencephalic and neighboring areas. Investigations by the method of terminal degeneration have demonstrated that these connections can be traced anatomically.

A third field presenting many new problems is the cerebellum. By the use of electrophysiological methods Adrian, and Snider and Stowell, have demonstrated that not only proprioceptive but also tactile impulses reach the anterior lobe of the cerebellum and that there exists a somatotopic localization within this and in the paramedian lobule. In addition also optic and acoustic impulses have been shown to impinge on the cerebellum. However, we do not know the pathways utilized in the transmission of the different kinds of impulses and consequently the phenomena are not yet fully intelligible. There is little doubt that continued anatomical studies, particularly when the method of terminal degeneration is utilized, will in time be able to give us the key to full understanding of the findings. Thus certain anatomical data favor the assumption that tactile impulses are mediated via the lateral reticular nucleus of the medulla oblongata. Again it was the method of terminal degeneration which made it possible to attack the problem. It may be permissible to mention in this connection that studies now in progress in our laboratory by means of the method of terminal degeneration and the modified Gudden method have revealed the presence of some hitherto doubtful or even un-

known pathways from the spinal cord to the cerebellum. Indeed, there appear to be far more such connections than is commonly realized. Thus neuroanatomical findings of this kind may in their turn present the physiologist with new problems and materially influence his interpretations of experimental data.

The examples mentioned so far are instances where the question of details in nervous connections are concerned. Attention has already been drawn to the need for quantitative determinations of cells and fibers. Many instances may be quoted of investigations of this kind which have brought forth data of supreme importance for the analysis of function. Lassek's studies of the Betz cells and the fibers of the pyramidal tract, Le Gros Clark's and Chacko's analyses of the lateral geniculate body in monkey and man, studies of the intraneural topography of human peripheral nerves by Sunderland and others, and Rexed's work on spinal nerve roots in man, are here mentioned as random examples from a steadily growing body of investigations of this type.

We need scarcely doubt that careful and systematically pursued anatomical investigations will in the future be able to furnish a wealth of new and valuable information of the finer organization of the nervous system. It would be sufficient to mention some publications of the last few years to support this statement. It is a fact worthy of notice that neurophysiological as well as neuroanatomical studies bear witness that the nervous system is far more complex than was dreamt of only a few years ago. Indeed, there may be some justification for the statement that in our views on the nervous system an almost revolutionary change has taken place. The demonstration by electroencephalography that the nervous system is never completely at rest may be mentioned as one of the most important contributing discoveries. That at any time some nerve cells are always discharging is indeed a fundamental feature apt to exert a profound influence on our views, as is also the concept of nervous impulses traversing closed neuronal chains. The importance of the latter phenomenon has been repeatedly stressed by Lorente de No and others, and appears to have been most recently demonstrated experimentally by Chang in the case of the thalamocortical interconnections. These and other findings have largely contributed a dynamic aspect to our ideas of the nervous system and they have greatly stimulated the elaboration of new hypotheses of cerebral function, for example explanations of the neural processes underlying such phenomena as memory, the ability to perceive universals, processes of learning and the like. A better knowledge of the structure of the brain, more particularly of the details of its neuronal interconnections, would greatly enhance our possibilities of judging the value of the different theories set forth on the function of the brain. If we are to decide whether Wiener and others are right in comparing the principles governing the action of the nervous system with those at work in modern electronic computing machines and if we are to consider it a general feature that neuronal chains are arranged in closed circuits, then a wealth of precise information of the organization of

the nervous system is still needed. The new science of "cybernetics" has no difficulty in finding instances of "feed-back" in the nervous system, but if this can be considered a general principle remains to be proved. For the solution of these and many other problems a close cooperation of neuroanatomy and neurophysiology is essential.

It is gradually becoming evident that, among all those fields of research which are devoted to the nervous system, it is from these two in collaboration that we may in future expect the most decisive and valuable contributions to a wider knowledge, in spite of the fact that they both utilize chiefly animal material in their investigations. We have to realize that what is needed today in neurologic research is information of details, thousands of details, if we are to fill the many gaps in understanding of the nervous system, and these details can be procured only by extensive series of experimental investigations.

This emphasis on the value of experimental research does not imply any underestimation of the other branches of neurologic research. In spite of the innumerable features of the organization of the nervous system common to man and experimental animals, there are certain aspects of nervous function which cannot be elucidated by animal studies. The chief objective of the clinical study of the nervous system of man are these aspects of nervous function. while the principal, fundamental features yield themselves more favorably to experimental research. Needless to say, clinical research will have to be based on the evidence brought forward by experimental animal studies to an increasing degree as progress is made in our understanding of form and function of the nervous system. On the other hand it is equally clear that results of clinical research will necessarily influence problems in the basic sciences and will point to research projects of fundamental importance.

Turning now to a brief consideration of the relation of neuroanatomy to the clinical aspects of neurologic research, let us first direct our attention to clinical neurology. As is well known, the clinical diagnosis of a morbid process affecting the nervous system is based on a knowledge of its structural and functional organization. Clinical neurology, therefore, will be interested in findings made in experimental neuroanatomy. This will be the case particularly where more marked differences exist between the human and animal nervous system. Human neuroanatomy will have as its material of study normal brains as well as brains with certain lesions, particularly more circumscribed ones.

To illustrate the relation of neuroanatomy to clinical neurology, the mention of a few instances where neuroanatomical studies have been of clinical importance will suffice. The method of trigeminal (medullary) tractotomy developed by Sjøqvist is a case in point. It is based directly on anatomical studies of the course and diameter of the trigeminal fibers combined with knowledge of certain functional features. Other more recent achievements in neurosurgical techniques are likewise the outcome of a fortunate combination of anatomical, physiologic and clinical observations, as for example the

method of transection of pain fibers in the spinal cord (anterolateral chordotomy) or at higher levels of the brain stem (so-called mesencephalic tractotomy). The same considerations are true with regard to recent attempts to treat involuntary movements and tremors by surgical procedures applied to the central nervous system. In the autonomic nervous system a detailed knowledge of the anatomical features is indispensable for the proper evaluation of the origin of the symptoms and for the planning and performance of successful therapeutic measures, a fact reflected, for instance, in the various operative procedures which have been employed in the treatment of essential hypertension, angina pectoris and other affections. A reliable interpretation of symptoms and the choice of adequate therapeutic procedures in cases of peripheral nerve lesions requires a full knowledge not only of the course of these nerves, but also of their fiber composition and of factors determining the power of regeneration of nerve fibers, subjects which have recently been studied extensively, particularly by Sunderland, Weiss and Young. Among other fields of anatomical research which have proved to be of fundamental importance to clinical neurologic views, one example is the pyramidal tract, considered to be the chief pathway for willed movements. Lassek's painstaking studies on the fiber composition of the tract and on the numerical relations between its fibers and the number of Betz cells in the motor area have resulted in a fundamental and highly desirable revision of our conceptions of this tract, formerly considered so simple.

The great development of the neocortex in man makes studies of human material essential in the study of cortical structure and connections. Many problems concerning the cerebral cortex are of even greater concern to psychiatry and psychology than to neurology. The understanding of the importance of neuroanatomy for these disciplines has been immensely prompted by the elaboration of the recent operative procedures on the cerebrum in certain types of mental derangements. The signs and symptoms following prefrontal lobotomy have convincingly demonstrated how mental functions are dependent on a material substratum for their correct performance. Here we are as yet only starting to realize dimly certain relations between particular parts of the brain and various sides of mental life. Another outcome of prefrontal lobotomy is the additional evidence that mental functions are by no means dependent solely on the cerebral cortex. Clinical as well as numerous neurophysiologic studies also indicate a very intimate correlation between the cortex and lower subdivisions of the nervous system with regard to these functions. Anatomical data for a full understanding are as yet not sufficient, but the detailed studies of brains from patients subjected to lobotomy, particularly by A. Meyer and his associates, as well as M. Meyer's studies by the method of terminal degeneration, have shown that these problems can be solved. It is interesting in this connection to recall that the most recent supplement of the psychosurgical repertoire, the isolated destruction of the dorsomedial nucleus of the thalamus, is a direct outcome of anatomical and physio-

logic research, which has demonstrated that the interruption of connections between this nucleus and the cerebral cortex is an essential point in the mechanism of lobotomy.

With regard to the cerebral cortex proper the minute parcellation arrived at by older anatomists has recently fallen into disrepute owing to criticisms chiefly by Lashley and Clark, a criticism welcome to those research workers who tend to emphasize the function of the cerebral cortex as an entity, and thus to reduce the functional importance of the subdivision of the cortex into smaller units. This criticism also tends to invalidate the Vogts' theory of pathoclisis, since this theory rests on the working hypothesis that each small cortical area and the minor subdivisions of other gray masses possess different functional qualities, and that these differences between the so-called topistic units are in the end responsible for their different vulnerability toward various morbid processes, and consequently determine the localization of a particular process. Lashley and Clark's criticism is certainly well founded, particularly their point that uniform criteria in the making of cyto-architectonic maps have been lacking. However, when one has had the opportunity to see how extremely sharp and precise the borders between adjoining cortical areas may present themselves in silver preparations when the afferents to one of them have degenerated, while those to the neighboring area are intact, then one can scarcely avoid believing that the principle of a distinct areal parcellation advocated by the classical workers in the field is in principle correct, even if the study of the cortex in Nissl preparations does not allow precise fixing of the limits and thus makes the resulting pattern of parcellation equivocal. Studies on the cerebral association fibers point in the same direction, although they have so far been performed only with the Marchi method. From an anatomical point of view the vast subject of associational connections of the cerebral cortex is as yet almost virgin territory. Neurophysiologic studies by the strychnine method (physiological neuronography) by McCulloch and collaborators lend support to the conception gained from anatomical studies, that the associational connections are extremely abundant but yet very specific. However, the physiologically established interareal connections should be anatomically verified, since there is still some uncertainty whether the strychnine evoked potentials never traverse synapses.

There still remain many problems in neuroanatomy which have considerable relevance to psychiatry and psychology. Our knowledge of the cerebral cortex, its synaptology and its connections with lower parts of the nervous system is still only in its beginning. But there is little doubt that investigations employing the method of terminal degeneration will prove fruitful. The data elicited so far tend to show that these connections are extremely specific. From a morphologist's point of view, one can scarcely escape the assumption that the cortical parcellation and the specificity of the intracortical connections must imply that each small area has its particular function, even if at present we do not have the means which permit us to analyze the functions of

individual areas and even if we must presume that they always collaborate in an integrative manner. Regardless of whether continued studies will show that the structural specificity is greater or less than we are inclined to believe today, this will not imply that the theories on the function of the brain as a whole are invalidated.

Just as neuroanatomy is of importance to psychiatry and psychology, it also furnishes the necessary basis for neuropathology. This is true particularly with regard to the problem of the separation of structurally differing areas which display a dissimilar liability to be involved in various disease processes. In addition to studies of fiber connections essential for the determination of which changes are secondary and which primary, cytochemical investigations of the normal nervous system will be of particular interest to neuropathology. We may hope that studies of this kind may contribute to an explanation of the selective vulnerability of different regions of the brain, and to throw some light on the processes occurring in the nerve cells in morbid conditions. Investigations on cytochemical changes occurring in nerve cells following transection of their axones by Bodian and collaborators and the finding of similar alterations in cortical nerve cells in some cases of cerebral atrophy seem to indicate that studies of this kind may be of value.

In the preceding discussion findings have been mentioned repeatedly pointing to a far-reaching correlation between mental functions and certain parts of the nervous system. We have for some time been familiar with the fact that changes in the body fluids may influence mental activities. It is sufficient to recall the effects of hypoxemia or the importance of thyroxin or sex hormones to make this clear, and numerous other examples might also be quoted. To the increasing amount of such observations on body-mind interrelationships is certainly due the growing orientation in a somatic direction which we have witnessed in psychiatry and to some extent in psychology in recent times. Such findings, furthermore, will have to form the basis of the so-called psychosomatic medicine.

Regrettable though it is, it can be understood that research workers in the field of neurology have been accused of considering mental processes from a crudely materialistic point of view and of being inclined to explain them as purely organic phenomena. However, all critical scientists will probably agree that, regardless of how far we may once reach in the correlation of mental with bodily functions, this knowledge will never permit us to solve the question of whether man possesses an immortal soul. This is and will always remain a question of faith. There is, therefore, no true antagonism between religion and neurologic research. Nobody need take offense that neurologic research approaches these questions along the only road available with its methods, the material one.

It has been possible to consider only some aspects of the role of neuroanatomy in neurologic research. However, brief as has been the documentation, we have shown that neuroanatomy is of basic importance to all these

fields of research. The other branches of neurologic research cannot be without neuroanatomy. It would be just as futile, however, if neuroanatomy were to work in isolation. Since, as we have already mentioned, studies of structure without consideration of function are of little value, the neuroanatomist will have to uphold a steady and intimate contact with other fields of neurologic research and to be aware of their progress and their problems. In this way he will not only receive valuable impulses to tackle particular research tasks, but what is of equal importance, his total view on form and function of the nervous system will be materially widened and have a broader perspective than would be the case without such contact.

Our present-day knowledge of the structure of the nervous system can be considered as no more than a very modest beginning. Consequently neuroanatomy has an enormous program of work ahead of it, because the tasks to be solved, numerous as they are, require extensive series of experiments and time-consuming methods of anatomical study.

In many instances we are still unable to achieve complete agreement between anatomical data and observations on the functions of the nervous system. As far as anatomical data are concerned we may be allowed to maintain that, provided the observations have been made with reliable methods, the findings themselves must be attributed the greatest importance. With the qualification that the available data may be misleading because they are not yet exhaustive enough, we shall have to agree with Spielmeyer when he said: "An established anatomical fact is not to be shaken."

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I believe all anatomists have divided the nervous system into the cerebrospinal and the sympathetic. The first of these is represented in this plate by M. Mance: it consists, first, of the cerebrum and cerebellum; secondly, of sentient nerves, which pursue their course to them, and of motor nerves, which proceed from them, either along the base of the brain, or along the spinal marrow, and then along every external part of the animal frame. The second is partly represented in this other plate, by the same anatomist: it comprehends, the internal ganglionic or sympathetic.

To these two subdivisions of the nervous system, I believe a third must be added, before our views of that system can be considered as at all complete;—it is one which I claim the merit of first pointing out in all its fulness. Suppose the cerebrum and cerebellum, the *centre* of the first subdivisions of the nervous system, and the ganglionic, or the second subdivision of this system, removed, *this remains*. It consists of the *true* spinal marrow, distinguished from the sentient and motor nerves which run along its course, as an *axis* of *excitor* and *motor* nerves. It is the seat of a peculiar series of physiological phenomena and a peculiar class of pathological affections.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases,* published in 1876.

Alterations of Basal Ganglion Tremor During Sleep

Walter J. Friedlander, M.D.

THERE are many facets to the problems involved in tremor that are not fully understood. One of these is what happens to parkinsonian tremor during sleep. In an attempt to understand this factor the following project was carried out, and in so doing several other aspects of tremor were also noted.

TECHNIQUE

Six patients with evident basal ganglion disease were used as the experimental group and four individuals with no basal ganglion disease were used as controls. All the patients were young or middle aged adult males. Tremor was measured[1] by placing a small Alnico magnet taped to the tip of the middle finger in close proximity to a wire coil; the coil in turn was connected to the input of a Grass electroencephalograph. Hence, any movement of the finger caused the magnet to move, changing the magnetic field; this was picked up by the wire coil, relayed to the electroencephalograph and thus recorded. Using this technique had the advantage not only of giving an easily readable and timed record, but also of permitting study of the electroencephalogram and the conscious state of the patient simultaneously. In two of the experimental group and all four of the control group, not only a resting tremogram was obtained but also a postural tremogram. The apparatus for each of these is illustrated in figures 1 and 2.

A resting tremor was obtained on each patient and then, without changing his position, he was put to sleep by an intravenous injection of 0.5 gm. of sodium Amytal. The depth of sleep was measured by the electroencephalogram and was considered optimum when "sleep spindles" became evident.[2] The rate of tremor was noted by counting the number of vibrations recorded in two seconds; this was done four times over a period of 14 seconds, and the average of these figures was noted (figures 3 and 4).

From the neurology section, U. S. Army Hospital, Fort Bragg, North Carolina.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 13, 1951.

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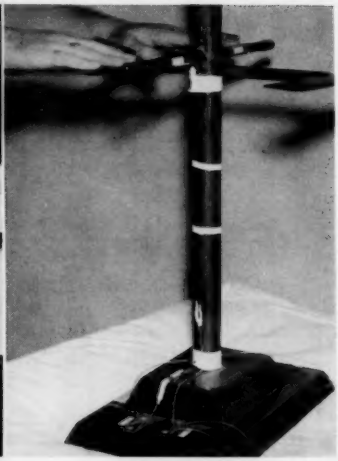
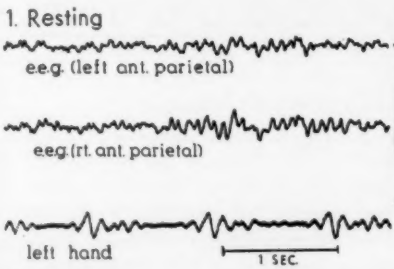


FIG. 1. *(left)* Method of obtaining resting and sleep tremor. FIG. 2. *(right)* Method of obtaining postural tremor.



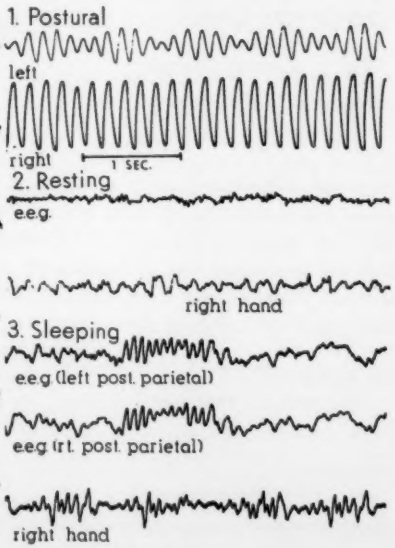


FIG. 3. *(left)* Sample tracings of resting and sleeping tremor.

FIG. 4. *(right)* Sample tracings of postural, resting and sleeping tremor of another patient.

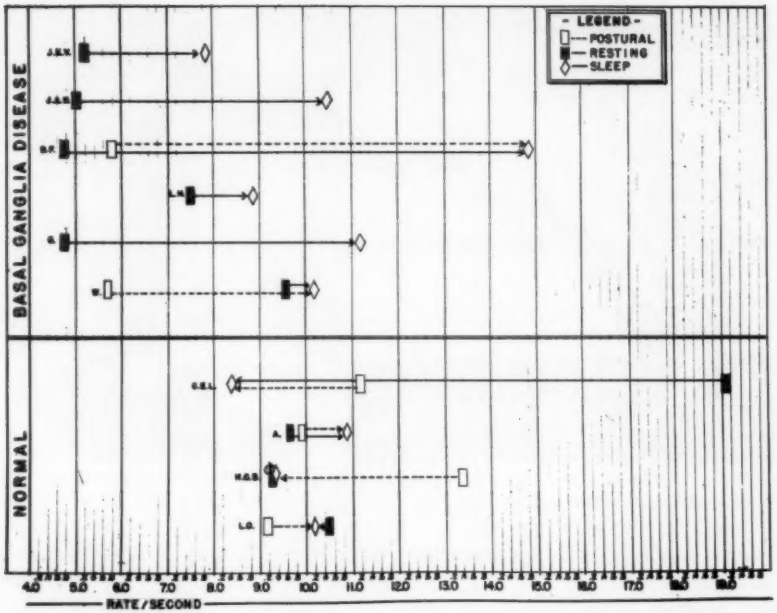


FIG. 5. Summary of results.

FINDINGS

The findings are summarized in figure 5. The range of frequency for the control group's resting sleep tremor is between 8.4 vibrations per second and 10.9 vibrations per second. In patients with basal ganglion disease, the frequency of tremor during sleep is within the range of 7.9 vibrations per second and 14.9 vibrations per second. In other words, even though the basal ganglion tremor during rest is significantly slower (average of 6.2 vibrations per second) than the rest tremor of the normals (an average of 12.1), the basal ganglion tremor during sleep becomes rapid enough so that it approximates the frequency of the normal tremor during sleep, which in turn is probably not significantly different than the normal tremor while awake.

The tremors that were obtained during sleep could not be seen by gross visual examination.

DISCUSSION

Though Parkinson[3] noted a persistence of tremor in advanced cases of "shaking palsy" during sleep, many authors[3–8] comment on the disappearance of tremor during sleep. It would seem from the present study that the slow typical tremor does disappear during sleep, although the cases may not have been at an advanced enough stage. However, of greater interest was the fact that a

tremor did appear during sleep whose characteristics were indistinguishable from the tremor of the control group during sleep, which in turn was the same as the control group while awake. This suggests that the maintenance of parkinsonian tremor is dependent upon central nervous system centers that maintain wakefulness, although "normal" tremor is not dependent upon such control. It is not possible to state whether the role of the "wakeful centers" in parkinsonian tremor is a direct one or acts secondarily through the cortex or other areas.

In the present studies several other facts were noted in the course of making the primary observations. The alpha frequency of the waking electroencephalogram, though frequently resembling the frequency of the tremor, is not identical with it; also, unlike Jasper and Andrews[9] no "spindles" were found in the tremor during sleep that corresponded with the "sleep spindles" in the electroencephalogram. This is in agreement with the statements of Schwab and Cobb[10] and Lindquist[11] that there is no direct or evident relationship between the electroencephalogram and tremor. The other fact noted is the difference between a resting tremor and a postural tremor. This is, of course, not a new observation, but the literature frequently does not make this distinction nor is it usually noted in the clinical examination.

SUMMARY

1. The resting tremor of patients with basal ganglion disease was compared with that in a normal control group while awake and while asleep.

2. The slow tremor of basal ganglion disease disappears during sleep but is replaced by a tremor of similar rate to that seen in normals during sleep.

3. It is suggested that central nervous system centers maintaining wakefulness have a role in the production of parkinsonian tremor which they do not have in the maintenance of normal tremor.

4. There seems to be no relationship between the electroencephalographic pattern and the frequency of a tremor.

5. Cognizance should again be taken of the difference between a resting and a postural tremor.

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A New Curare Antagonist in Electroshock Therapy

Albert Faulconer, Jr., M.D., Edward H. Lambert, M.D. and Howard P. Rome, M.D.

THE DESIRABILITY of a safe, quick and effective antidote to curare in clinical anesthesia is obvious. The use of Prostigmine (neostigmine) in this capacity has been a common practice almost since the introduction of curare as a muscular relaxant in the practice of anesthesia. This drug, however, produces undesirable and sometimes alarming side reactions which are manifestations of its potent muscarinic properties. Furthermore, its use in cautious intravenous doses (0.5 mg. Prostigmine methylsulfate) as an antidote to curare restores function less quickly than is needed in many clinical situations.

PRELIMINARY WORK

Favorable reports[1,2,3] from other laboratories and surgical services on the trial of a new drug called Tensilon suggested a program for the clinical trial of this drug in the anesthesia service. A trial dose of 5 mg. of this new agent was administered intravenously to one of the authors after he had been curarized with a total of 12 mg. of d-tubocurarine. The restoration of motor function resulting from this small dose of Tensilon was quick and gratifying to the subject, and was without noticeable side effects.

Therefore, a series of electromyographic studies on patients undergoing electroshock therapy was made by a procedure similar to that described by Harvey and Masland.[4] Surface electrodes over the abductor digiti quinti muscle of the hand were used to record the action potential of this muscle. The muscle was stimulated periodically by a series of 8 to 10 supramaximal electric shocks at a rate of 5 per second applied to the ulnar nerve at the wrist. The action potential was observed and photographed on a cathode-ray oscillograph screen (figure 1). Since the nerve was stimulated supramaximally, the amplitude of the action potential is a measure of the number of muscle fibers activated. The amplitude of the action potential declines when the number of active fibers is reduced by block of neuromuscular junctions by d-tubocurarine. In subsequent figures, the amplitude of the first and

From the sections of anesthesiology, physiology, and neurology and psychiatry, Mayo Clinic, Rochester, Minnesota.

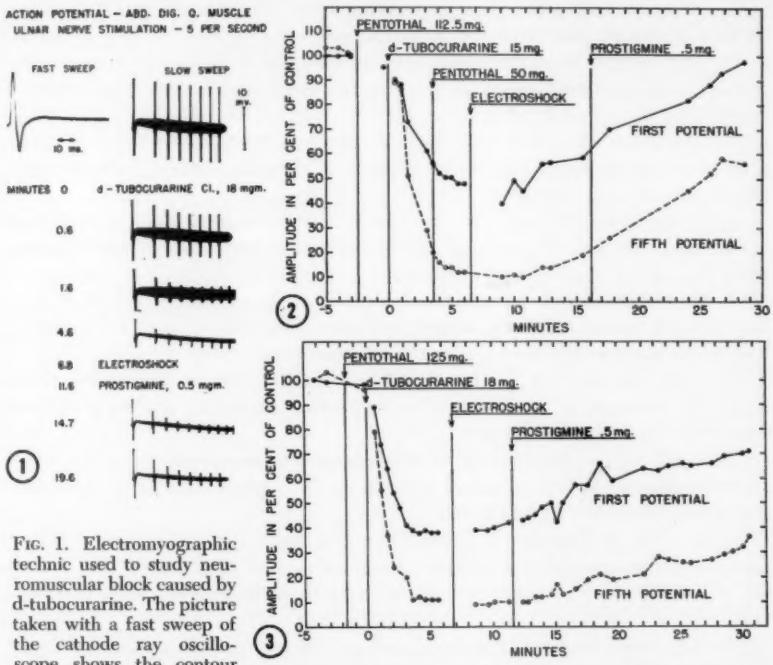

FIG. 1. Electromyographic technic used to study neuromuscular block caused by d-tubocurarine. The picture taken with a fast sweep of the cathode ray oscilloscope shows the contour of the action potential of the abductor digiti quinti muscle of the hand after supramaximal stimulation of the ulnar nerve. The pictures taken at a slow sweep show the amplitude of the potential during repetitive stimulation of the nerve at 5 shocks per second. Note that d-tubocurarine reduces the initial response of the muscle and causes a progressive decline of the potential with the first few shocks. The latter decline is related to the inability of curarized muscle to maintain a tetanic contraction.

FIG. 2. Approximately five minutes is required for maximal neuromuscular block to develop after the injection of d-tubocurarine. In this instance the person concerned weighed 175 pounds and was 48 years old. There was no respiratory embarrassment. The muscular contraction was graded 2 to 3.

FIG. 3. Insignificant effect of 0.5 mg. of Prostigmine on neuromuscular block in this patient. There was no respiratory embarrassment. The muscular contraction was graded 2.

fifth potentials of each series of shocks at a rate of 5 per second has been used as a measure of the degree of curarization during the procedure of electroshock therapy.

Using this technic, neuromuscular conduction was studied in nine patients during 19 electroshock treatments. All patients undergoing electroshock received a premedication dose of 1/150 gr. of atropine sulfate.

The following conclusions were derived from these studies:

1. A state of curarization can be achieved safely which will ensure the

patient against traumatic damage resulting from the convulsion which seems to be a necessary part of electroshock therapy.

2. This degree of curarization can be achieved without seriously imposing upon the patient's ability to react to the electroshock with a generalized convulsion.

3. The dose of curare necessary to produce the desired result is most often, but not always, 3 mg. of d-tubocurarine chloride pentahydrate for each 25 pounds of body weight.

4. If the dose of curare is administered intravenously over a period of 30 seconds, the time of maximal paralytic effect is very close to five minutes after the end of the injection (figure 2).

5. Pentothal sodium administered rapidly in an amount equal to 25 mg. for each 25 pounds of body weight will often, but not always, be sufficient to provide satisfactory amnesia for the treatment.

6. After electroshock produced at the depth of curare depression, there is a slow recovery of neuromuscular conduction extending over a period of more than 30 minutes (figure 2).

7. If 0.5 mg. of Prostigmine is administered intravenously after the electroshock, the period of recovery appears to be slightly shortened, although not dramatically so (figures 2 and 3).

8. If 5 mg. of Tensilon is given, there is a rapid but incomplete recovery from the electromyographic change brought about by the curare. This recovery is accompanied by some clinical manifestations of recovery from curarization.

9. If a larger dose of Tensilon, such as 2.5 mg. per 25 pounds of body weight, is administered, there is electromyographic evidence of almost immediate and substantial return from the curare depression. This is manifested by clinical evidence of nearly complete recovery (figures 4 and 5).

10. If 0.5 mg. of Prostigmine is combined with Tensilon, no significant difference is seen in the electromyographic recovery from the condition in which optimal doses of Tensilon are used alone (figure 6).

In the course of these preliminary studies there was no evidence of ill side effects from the use of Tensilon, such as the undesirable parasympathomimetic effect.

CLINICAL APPLICATION

As a result of these findings, the following tentative program was set up for the management of patients who are to undergo electroshock therapy in whom any suspicion of myasthenia gravis had been ruled out by neurologic consultation. At the time of the first treatment and after premedication with 1/150 grain of atropine sulfate, the patients received a test dose of each of the drugs used in the following amounts: solution of Pentothal sodium, 1 cc. (25 mg. thiopental sodium) with a one minute observation period; solution of d-tubocurarine, 1 cc. (3 mg. d-tubocurarine chloride pentahydrate) with a

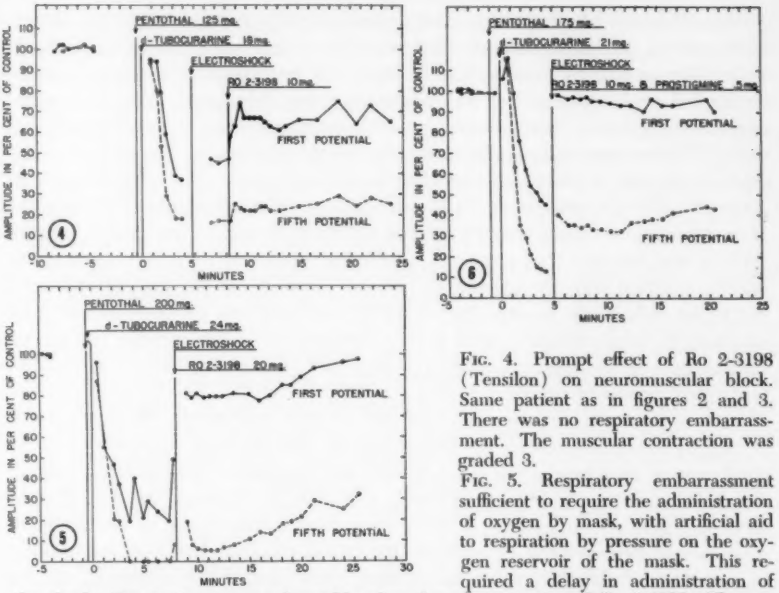

FIG. 4. Prompt effect of Ro 2-3198 (Tensilon) on neuromuscular block. Same patient as in figures 2 and 3. There was no respiratory embarrassment. The muscular contraction was graded 3.

FIG. 5. Respiratory embarrassment sufficient to require the administration of oxygen by mask, with artificial aid to respiration by pressure on the oxygen reservoir of the mask. This required a delay in administration of the shock. Respiration improved quickly after the administration of Ro 2-3198. The patient weighed 215 pounds and was 32 years old. The muscular contraction was graded between 0 and 1.

FIG. 6. Prompt effect of Ro 2-3198 on neuromuscular block. It is doubtful that Prostigmine contributed much to the response (see figure 2). The sequence of drug administration in this record is that recommended for routine use after initial tests to rule out hypersensitivity of the patient to the drugs used. Same patient as in figure 2. There was no respiratory embarrassment. The muscular contraction was graded 1 to 2.

three minute observation period; and Tensilon, 0.25 cc. (2.5 mg. m-hydroxy phenylethyldimethylammonium bromide) with a two minute observation period.

If there were no untoward reactions to these trial doses, as manifested by the patient's response to tests such as that of ocular convergence, degree of narrowing of the palpebral fissure, ability to swallow, ability to lift the head and strength of the grip, the following procedure was adopted. The dose was determined for each patient on a basis of weight. For each 25 pounds of body weight, the dose computation was 25 mg. of Pentothal sodium, 3 mg. of d-tubocurarine, and 2.5 mg. of Tensilon. A minimal total weight for all adult patients was considered to be 100 pounds, and a maximal total weight for all patients was considered to be 200 pounds. Thus, the smallest dose of solutions of Pentothal sodium and d-tubocurarine administered to any adult patient would be 4 cc. of each, and the largest dose of either of the drugs, in solution form, administered to any patient, regardless of body weight, would be 8 cc. of each.

The time of administration was as follows: First, the solution of Pentothal sodium was administered intravenously within a period of 15 seconds as rapidly as feasible. Immediately after this injection the syringe was disconnected and replaced by one containing the calculated dose of d-tubocurarine in solution; this solution was administered over a period of 30 seconds. This syringe and needle were maintained in place in the patient's vein, and at the end of three minutes the electroshock technician was allowed to proceed with the placement of the electrodes. Four and one half minutes after the end of administration of the solution of curare, the empty curare syringe was disconnected from the needle and replaced by a syringe containing the solution with the calculated dose of Tensilon. If the patient appeared not to be sufficiently anesthetized, a little more solution of Pentothal sodium (3 to 5 cc.) was injected prior to the attachment of the syringe containing the solution of Tensilon. A blood pressure cuff on the same arm was inflated to prevent access of the drug to the general circulation. The solution of Tensilon was injected into the vein and the syringe and needle were removed. At exactly five minutes after the end of the administration of solution of curare, electroshock was produced. If a satisfactory reaction (convulsion) ensued, the blood pressure cuff was deflated, allowing the solution of Tensilon to enter the general circulation. However, if subsequent shock or shocks were necessary to produce the convulsion, the blood pressure cuff was maintained in a state of inflation until a satisfactory result had been observed, or the treatment had been suspended. This use of the blood pressure cuff technic has proved to be very useful and now constitutes routine practice.

With this method 18 patients underwent a total of 97 electroshock treatments. The following observations were recorded for each treatment:

1. The age and weight of the patient.
2. Satisfactory or unsatisfactory convulsion.
3. The resistance of the patient's arm on passive flexion and extension of the elbow during the convulsion was noted, and was graded 0 to 4+ by the anesthetist. Grade 0 designated complete absence of resistance, while grade 4+ indicated marked resistance to passive motion.
4. Respiratory embarrassment: whether or not it was present as manifested by difficulty in breathing, excessive depression of respiration or cyanosis.

RESULTS

The results of these observations may be summarized as follows. Eighteen patients were studied: 13 were female, five were male. Their ages ranged from 32 to 69 years, and their weights ranged from 88½ to 215 pounds. The number of electroshock treatments administered to each patient ranged from three to nine, with a total of 97. Of the 97 treatments, 91 were considered to have produced convulsive reactions that were satisfactory. One patient failed to react to three out of four treatments, one failed to react to one out of six treatments, one failed to react to one out of eight treatments and one

failed to react to one out of six treatments. In grading the resistance to passive flexion extension of the forearm during convulsions, results of 10 treatments were graded as 0, 27 as 1+, 25 as 2+, 16 as 3+ and 13 as 4+. No reports were recorded in six of the treatments.

Respiratory embarrassment was observed during five of the 97 treatments, occurring in two of the 18 patients. Three of these occurrences were reported for one patient who underwent a total of four treatments; two were observed in another patient who underwent a total of six treatments.

COMMENT

In reviewing these results, it is apparent that overcurarization occurred in two of 18 patients. Both of these experienced excessive respiratory depression. They also were reported as having a preponderance of grade 0 or 1+ estimates of resistance to the flexion-extension test. It is concluded that the dose of solution of curare for these patients was excessive. It is of interest to note that these two patients were among the heaviest patients in the series; one weighing 215 pounds and the other 183 pounds. At the other extreme, two of 18 patients in every instance were graded as having 4+ resistance to the flexion-extension test during the seizure produced by electroshock. These patients undoubtedly would have been better served with larger doses of solution of d-tubocurarine. In summary, the treatment was satisfactory for 14 of the 18 patients studied in this series.

This general treatment has been adopted as routine practice and has been followed in several hundred electroshock treatments. When necessary, doses of the drugs administered are adjusted as indicated by previous experience with the patient. However, the usual practice continues to be to administer 2.5 mg. of Tensilon to counteract each 3 mg. of d-tubocurarine. The largest dose of Tensilon administered in these studies has been 22.5 mg. Such large doses appear, in many cases, to produce a mild degree of salivation and some increase in perspiration.

For several months Tensilon has been used by members of the section of anesthesiology and intravenous therapy at the Mayo Clinic to counteract curare depression observed in patients undergoing surgical operations. On a few occasions, such use has been accompanied by an unexplained reduction in pulse rate. On rare occasions, particularly after prolonged anesthesia with Pentothal sodium, a disturbing reduction of blood pressure has followed the administration of Tensilon. On every such occasion, however, the decrease of blood pressure was accompanied by a marked increase in the respiratory ventilation rate; consequently, the reduction in blood pressure may have been a manifestation of a sudden decrease of carbon dioxide tension.

Actual measurement of the respiratory ventilation rate of patients who have been curarized during surgical operations discloses marked increases within 90 seconds after the intravenous administration of 10 mg. of Tensilon. The increase was most often inversely proportional to the ventilation rate prior to the administration of the drug. Thus, within a 90 second period a

change from two liters to nine liters per minute ventilation after the intravenous administration of 10 mg. of Tensilon was observed.

Tensilon has been administered approximately 2,000 times to curarized patients without the occurrence of alarming side reactions in any instance.

SUMMARY

Electromyographic studies reveal, 1) that the maximal electromyographic change produced after the intravenous administration of solution of curare is observed approximately five minutes after the end of the injection; 2) that the normal recovery period after clinically useful doses of curare is in excess of 30 minutes; 3) that the intravenous administration of 0.5 mg. of Prostigmine five minutes after the administration of clinically effective doses of solution of curare very slightly accelerates recovery as indicated by the electromyogram; 4) that the administration of Tensilon in a dose of 2.5 mg. for each 3 mg. of curare administered five minutes previously produces a substantial return of the muscle action potential in less than 90 seconds which is maintained satisfactorily; 5) that the electromyographic restoration of function described above, as obtained with Tensilon, is accompanied by clinical manifestations of decurarization.

A technic for the administration of solutions of Pentothal sodium, d-tubocurarine and Tensilon in the management of patients undergoing electroshock therapy is described.

Tensilon administered intravenously in doses ranging from 10 to 20 mg. has been used to counteract serious curare depression after surgical anesthesia. The measurement of the respiratory ventilation rate of patients treated in this manner reveals a substantial increase in ventilation rate within 90 seconds after administration of Tensilon. On one occasion the ventilation rate increased from two to nine liters per minute.

In approximately 2,000 administrations of Tensilon during these clinical studies no alarming reactions were observed which could be directly ascribed to this drug. Minor reactions to doses as large as 20 mg. include excessive perspiration, mild salivation and, in the case of uncurarized patients who are awake, occasional abdominal cramps.

Tensilon, the drug used in this study, was supplied through the courtesy of Hoffmann-LaRoche, Inc., Nutley, N. J.

We are grateful to Dr. J. S. Lundy, head of the section of anesthesiology, the Mayo Clinic, for many helpful suggestions made during the course of this study, and to Dr. J. C. Doerr for his suggestion of the blood pressure cuff technic.

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Preliminary Study of a New Antiparkinson Agent

Lewis J. Doshay, M.D., Kate Constable, M.D. and Stephen Fromer, M.D.

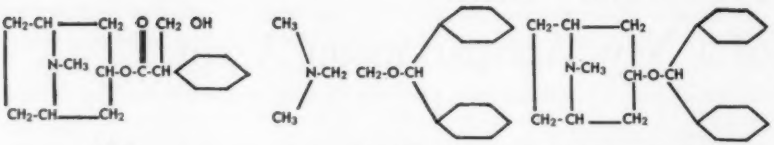
THE often discussed problem of the increasing size of our older population is intimately connected with any consideration of treatment of parkinsonism. The largest group of persons ill with this malady are classified as arteriosclerotic and are, therefore, a casualty of the aging process. The other two types of parkinsonism, that is, postencephalitic and idiopathic, likewise contribute substantially to the estimated million cases of parkinsonism, that we believe may be existent in this country. The problem presented by so large a section of the population ill with a disabling disease and the inadequacy of current therapy fully to control the ailment creates an ever-present need to search for new drugs.[1] In this setting we wish to present a report on a new synthetic agent, MK-02, which upon preliminary survey, has shown promise of being a valuable adjunct in the treatment of parkinsonism.

CHEMISTRY AND PHARMACOLOGY

For many years, atropine[2,3,4] and similar parasympatholytic preparations[5,6] have been used for the treatment of parkinsonism. Other preparations that have received considerable attention in recent years are Panparnit, Tolserol, Diparcol, Artane and the antihistaminics. Among the antihistaminics, Benadryl and Thephorin are being employed with some success in combination with belladonna alkaloids and Artane, and occasionally, alone. Since Benadryl and atropine alone and in combination have shown encouraging results, an agent incorporating the active portions of each molecule would be expected to give good results. Such an agent has been made available. Examination of the chemical structure of this new compound, MK-02, or tropine benzohydryl ether methane sulfonate, readily shows it to contain the tropine portion of the atropine molecule and the benzohydryl portion of the benadryl molecule.

In animal experiments it has been shown that tropine benzohydryl ether possesses both atropine-like and antihistaminic properties. In tests performed to counteract the histamine effect on the isolated strip of guinea pig's intestine and in intact guinea pigs in histamine aerosol chambers, MK-02 was found

From the Vanderbilt Clinic and the Neurological Institute, New York City, under the department of neurology of the College of Physicians and Surgeons, Columbia University.



Atropine Benadryl Tropine Benzohydral Ether

effective. In guinea pigs injected intravenously with histamine, MK-02 was shown to have an antihistaminic activity of an order equal to that of one of the more active antihistaminic preparations now available, Neo-antergan. Tests performed on the isolated guinea pig intestine, which had been previously exposed to tropine benzohydryl ether, indicated that acetylcholine applied to this organ was completely without effect. This parasympatholytic action of MK-02 was equal to that of atropine sulfate on a weight for weight basis.

MK-02 is extremely nontoxic. The acute toxicity in mice is approximately 87 mg./kg. Death in these animal subjects is preceded by mild clonic convulsions. In acute toxicity tests done on rats, the LD-50 was calculated to be 353 ± 40 mg./kg. When one considers these figures in light of the fact that the human dose is somewhere between 0.5 mg. and 5 mg., it can easily be seen that the therapeutic (tolerance) index of this agent is extremely high. Chronic toxicity studies done with tropine benzohydryl ether in two groups of rats at levels of .005 per cent and .01 per cent in the diet for 23 weeks were negative. In dogs given repeated doses, both by mouth and subcutaneously, up to 5 mg./kg. did not produce any evidence of toxic reaction or of any side effects except some mydriasis following doses greater than 1 mg./kg.

CLINICAL STUDIES

MK-02 was supplied in the form of 0.5 mg., 1 mg., 2 mg. and 5 mg. tablets to meet the varied needs and tolerance of the patients. A small group of 20 patients were maintained under close observation during the course of the study and the effects and side reactions were recorded. Most patients with postencephalitic parkinsonism exhibited excellent tolerance for the 2 mg. and some for the 5 mg. tablets. On the other hand, the majority of the arteriosclerotic patients fared best on 0.5 mg. or 1 mg. doses, and the idiopathic Parkinson cases for the most part received 1 or 2 mg. doses. As the study progressed, it was noted that MK-02 had a very prolonged action so that a number of patients were able to get along on as little as 0.5 mg. or 1 mg. a day. Some postencephalitic patients on the other hand used much larger doses for many months without a trace of ill effect. The cumulative action of the drug made it possible to maintain many patients on a twice-a-day therapy and some on once-a-day therapy. This proved of special advantage to those who disliked frequent medication. The chief side reaction of MK-02 was found to be dryness of the mouth, hence the patients were advised to

take the agent after meals. Those, of course, who had marked sialorrhea found no difficulty on this score.

After two months of explorative study, it became evident that in many cases MK-02 could not maintain the patient fully symptom-free by itself, the chief reason being that patients tended to become listless and somewhat depressed. Artane,[7,8] on the other hand, has considerable cerebral stimulating action. Therefore, in many of the patients, Artane was added to MK-02. Such patients fared well on the combination. Among patients who had been taking Artane and were switched to MK-02, the dose of Artane needed to supplement the MK-02 therapy was much smaller than that which they had previously required.

Since it usually took about three days for the cumulative action of MK-02 to manifest itself, patients were permitted to continue on their usual antiparkinsonism therapy when commencing treatment with MK-02. Nearly all patients began treatment by taking MK-02 twice a day in the dosages previously indicated for each category. Within a week after initiation of MK-02 therapy, it was usually possible to establish whether or not beneficial effects were being achieved and what the side reactions were. Reductions in the dose of Artane were generally accomplished at about this time. By a slow process of adjustment covering approximately one month, the dose and frequency of administration of Artane and MK-02 and the optimum level of tolerance and effectiveness of the combined therapy was determined. When these two drugs were employed, it was found preferable to administer Artane before and MK-02 after the meal.

RESULTS

In the original group of 20 patients who were followed for one year, there were eight arteriosclerotic, six idiopathic and six postencephalitic cases. The group was composed of 13 males and seven females ranging in age from 36 to 74 years. During the exploratory stage, some patients were given large doses of MK-02. The relaxant effect was so pronounced that those with advanced rigidity reported their limbs and neck were completely limp and flaccid within three days. Some could not raise the head off the pillow, nor lift an arm. After a day or two of continued therapy, however, most of these patients improved and felt freer of movement than on any previous medication. Others were quite disturbed by this preliminary relaxant effect and were frightened from continuing with the study. For this reason smaller doses of MK-02 were employed in later trials.

As with all antiparkinson drugs which patients receive over a continuous period of time, an increase in tolerance develops which leads to a decrease in the therapeutic effect of the medication. While this situation was encountered, some patients nevertheless seemed to derive sufficient benefit from MK-02 therapy, since upon discontinuing it they experienced an uncomfortable return of rigidity. Thus, eight of the original group of 20 patients re-

turned to Artane therapy alone, at one time or another during the study, and found it necessary to resume taking MK-02 along with the Artane. These two drugs seem to supplement each other very well. The following case will illustrate:

Case 1.—V. B., a 51 year old patient with idiopathic parkinsonism noted tremor and rigidity of the left side of the body and labored speech for two years. Bellabulgara caused disturbing side reactions. Artane treatment was started in October 1949 and had a favorable action for a time, but the effects wore off and the rigidity and tremor spread to the other side. The patient had to give up employment and was greatly depressed by his situation. MK-02, 1 mg. b.i.d., was added to Artane on January 10, 1951, and he felt freer in body, but remained disgruntled over domestic and unemployment problems and the added dryness of the mouth produced by MK-02. He discontinued it in March and soon began to feel much worse. He was hardly able to get about. On May 5, 1951, he returned to MK-02, 1 mg. b.i.d., and has done remarkably well since. On June 7 he ran out of his supply of MK-02 and three days later experienced severe rigidity and tremor. On resuming MK-02 he reported as follows: "I was like a changed man with the new medicine—before that my arms were so stiff and weak that I could not cover my body with the blankets during the night. When I became uncovered I felt chilled, restless, sweaty and could not lie in one position for more than an hour. With MK-02 I was able to move easier and could cover myself; I felt relaxed and slept right through the night, and in the morning I was rested and had a good feeling in the body that lasted all day. With the new medicine I can do work around my house, without it I can do nothing." He has continued in favorable condition on MK-02 and 2 mg. Artane t.i.d.

Movement is rendered easier with MK-02 and Artane therapy than when Artane is combined with Bellabulgara, hyoscine, stramonium or other agents usually employed in the treatment of parkinsonism. An example of this was reported previously.[7] After two years on Artane and Bellabulgara, the patient's tolerance increased to the extent that rigidity interfered with walking and he had to resort to the use of a wheel chair in order to get about. The addition of MK-02 seven months ago relaxed his limbs and spine sufficiently so that he gets about with fair comfort, this despite the fact that it was recently discovered he had been walking around with a pathologic fracture of one hip for three months.

An interesting action of MK-02 is its capacity to obliterate almost completely the typical parkinsonian facies. In most patients under treatment for about a week or two, the face becomes relaxed, smiling and more natural. This effect upon the well-known facial expression of parkinsonism proved especially gratifying to women patients, as the following case illustrates:

Case 2.—E. S., a 39 year old woman with postencephalitic parkinsonism, suffered from lethargy, sialorrhoea, oculogyria, rigidity and tremor. She was given atropine in 1942 and did fairly well until 1945, when drooling reappeared. Progressive increases in the dose of atropine failed to stem the flow of saliva and hyoscine was added to the course of therapy. Several months later one, two and then three tablets of Rabellon t.i.d. were administered but to no avail. She became increasingly rigid; the oculogyria appeared with disturbing frequency; and there was marked somnolence. Benzedrine was substituted without beneficial effect. Later Diparcol was tried but led to nausea and vomiting. Panparnit was tried and produced some beneficial effects until tolerance developed and it had to be discontinued. Thephorin had no effect and she complained of vomiting while taking it. She was

returned to Panparnit combined with atropine, but the original beneficial effect was not obtained. In June 1949 she was given Artane and atropine and did well for over a year, when tremor, sialorrhoea, muscular cramps, rigidity and sluggishness reappeared. In October 1950 MK-02 was substituted for atropine and she has been doing remarkably well until the present, on a dosage of 5 mg. MK-02 and 5 mg. Artane t.i.d. An interesting observation was that in January 1951 her supply of MK-02 was depleted and within three days sialorrhoea became extremely pronounced. Neither hyoscine nor atropine could control this condition. When MK-02 was resumed, the sialorrhoea was completely controlled within one day. This patient is particularly pleased with her improved facial appearance. She smiles naturally and her speech is freer. Her family and neighbors have commented on the favorable change in her appearance. She is also happy because she has none of the blurring of vision she used to experience while taking atropine.

MK-02 has a unique effect in relieving muscle cramps, such as the familiar cramping of the toes which is highly aggravating to many patients with advanced parkinsonism. It also relieves muscle spasm which produces the so-called "glued" feeling that many patients experience, when they suddenly find themselves frozen to the ground and cannot shift from the spot nor move a limb. Many patients in such predicament have been known to fall and injure themselves. Also, through its powerful relaxant effect, MK-02 has proved of special value in physiotherapy. The antispasmodic action of MK-02 was found particularly beneficial to some of the postencephalitic cases, who possess tolerance for large amounts of antiparkinson drugs.[9] The following case is an example:

Case 3.—E. R., a 36 year old patient with postencephalitic parkinsonism, was first seen in 1943 when she was extremely emaciated, weighed 82 lbs. and exhibited pronounced tremors, sweating, sialorrhoea, lethargy, oculogyria and rigidity. She had great difficulty in walking or standing. She was given atropine and hyosine, after which her condition improved remarkably, with her weight increasing to 101 lbs. She remained completely stabilized for four years, when the effects of atropine began to wear off. Panparnit was then added in small amounts but had no effect and large amounts caused stomach cramps. Artane was then tried without benefit. In August 1948 Diparcol was administered and she immediately responded with marked improvement. She continued to be comfortable until March 1949, when the beneficial effects of Diparcol wore off and cramping of the toes, crying, sleeplessness, tremor and rigidity returned to a degree equal to that originally noted. Benadryl was administered but made the patient more tremulous and upset her stomach. Thephorin was then tried and so was Artane; each failed. In August 1950 she was again given Diparcol and atropine, with hyoscine added, but she continued to feel wretched and her family suffered accordingly. In November 1950 MK-02 was first substituted for atropine and then for atropine and hyoscine. She has continued remarkably well to date on a combination of Diparcol and MK-02. She feeds and dresses herself, takes her dog for walks and talks more clearly. Her face is relaxed and she smiles more easily than on any previous medication. She has improved so much that she has been able to go swimming several times during the summer. On one occasion, she tried MK-02 without Diparcol for 10 days and her oculogyria became troublesome. On another occasion, her supply of MK-02 was depleted and within three days she became rigid, sleepless, tremulous, cried and suffered severe cramps in the arms and toes. On a dosage regime of 2 mg. of MK-02 and 62 mg. of Diparcol q.i.d. she is doing remarkably well.

It is very possible that after a period of time the beneficial effects of the combination of MK-02 and Diparcol will wear off, as has been the case with

other preparations this patient received previously. Situations of this type serve to emphasize why we need so many drugs to cope with the progression of symptoms and the ever-changing fancies, needs and tolerance of patients.

Tropine benzohydryl ether controlled sialorrhoea in most patients far better than even atropine and usually without the distress of a parched throat, difficulty in swallowing and loss of appetite. In three patients, however, the large doses of MK-02 required to control their other symptoms produced an uncomfortably dry throat, which led them to discontinue taking this drug.

An important finding that recently came to attention was the ability of MK-02 to control severe tremor. This is significant because such tremor is often totally resistant to all presently available therapy and has been a most challenging problem in the treatment of parkinsonism. This effect on severe tremor has been especially beneficial to older patients, who generally exhibit the worst form of tremor. The following two cases are offered as examples of severe tremor that were benefitted.

Case 4.—L. T., a 59 year old patient with arteriosclerotic parkinsonism, has had advanced tremor and rigidity of the extremities for the past four years. Artane alone failed to control symptoms although it helped for over a year. In April 1951 MK-02, 1 mg. t.i.d., was added to his regime of therapy. His wife reported remarkable changes for the better: "Before, my husband would get out of bed ten times a night because he was tense, restless and shaking—now he sleeps right through the night. Before, he avoided people because it took him so long to say a few words and he had to shift his position every five minutes. Now he talks and smiles so easily that he looks for company; he is calm in mind and the tremor is gone. He can sit and read a paper for hours at a time." The patient has maintained his improved status on 2 mg. of Artane and 1 mg. of MK-02 t.i.d.

Case 5.—H. F., a 61 year old patient with arteriosclerotic parkinsonism, became ill three years ago with tremor and rigidity of the left side that spread to the right. Phenobarbital was administered without beneficial effect. Benadryl produced too much dryness, and hyoscine caused mental blurring. Artane failed to control the tremor and sleeplessness. MK-02 was added to Artane in May 1951, in the dose of 1 mg. t.i.d., and caused marked dryness of the throat. This was reduced to 1 mg. on retiring and led to a remarkable improvement. The patient reported: "In 15 minutes after taking the pill I feel relaxed in the entire body, fall asleep and feel rested until the following noon. Before my hands would shake so much that I couldn't help watching them and couldn't fall asleep. Even if I did, I would have nightmares and restlessness and would feel miserable the next day."

Of the 20 cases in the original group under treatment with MK-02, 13 were improved above and beyond Artane, or Artane in combination with Bellabulgara, hyoscine, Rabellon, Benadryl, Thephorin, Panparnit and other drugs. Among the seven failures, three terminated treatment because of excessive dryness and two presented the problem of a personality disorder with depression and discouragement under all types of medication. These two offered weakness as the chief reason for terminating treatment. The remaining two cases showed no improvement with MK-02 and were returned to their previous regime of therapy. It is probable that had we known more regarding the dosage at the outset of the investigation, some of these failures might have been prevented.

TABLE 1

SIDE REACTIONS WITH MK-02 COMPARED WITH OTHER DRUGS

	MK–02 62 Cases		*Artane* 117 Cases*		*Atropine* 112 Cases*		*Scopolamine* 117 Cases*		*Belladonna Products* 117 Cases*		*Panpanit* 26 Cases*	
Type of Reaction	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Dryness of mouth	11	17	14	12	104	93	21	18	52	44	1	4
Blurred vision	3	5	6	5	92	82	5	4	31	27	–	–
Nausea or vomiting	0	0	1	1	12	11	1	1	7	6	3	11
Dizziness or giddiness	0	0	2	2	7	6	8	7	14	12	8	31
Dysphagia	3	5	–	–	4	3	2	2	9	8	–	–
Bladder hesitancy	0	0	–	–	2	2	–	–	3	3	1	4
Drowsiness	0	0	2	2	1	1	13	11	2	2	–	–
Mental depression	2†	3	–	–	2	2	3	3	4	3	4	15
Tachycardia	0	0	–	–	?	?	–	–	3	3	6	23
Adynamia or prostration	0	0	–	–	?	?	2	2	5	4	5	19

*From Table 6 of Doshay and Constable[7].

†Before we became aware that Artane was needed for cerebral stimulation.

On the basis of the above observations in 62 cases, it can be safely stated that MK-02 has less disturbing side reactions when employed in therapeutic dosage than many drugs in current use.

In a later publication we hope to present the outcome of treatment in a larger series of patients, which may permit a better evaluation of the results with MK-02 in terms of statistically significant figures. For the present we believe it is of sufficient importance to state that the new drug proved helpful in a majority of the cases and that a number of patients found greater relief with MK-02 than with any other available remedy. Favorable effects were especially noted in the control of rigidity, fixed facies, cramping of the toes, muscle spasm, sialorrhoea and severe tremor. On this basis, MK-02 is deserving of a place among drugs useful in the treatment of parkinsonism, especially because it is satisfactorily non-toxic.

SIDE REACTIONS

Since the large majority of side reactions produced by antiparkinson drugs are manifested within the first few weeks or months of treatment, it is valid to report on the untoward effects in a larger series of 62 patients now being observed. This larger group has been under survey for from one to six months. The outstanding side reaction caused by MK-02 is dryness of the mouth. This occurred in moderate degree among 17 per cent of the 62 patients treated thus far. In three cases dryness was of such severe degree that treatment was discontinued because of it. The frequency of dryness produced by MK-02 is about the same as that encountered with hyoscine, but whereas the latter drug also leads to complaints of somnolence and dizziness, no such reactions were noted among the patients taking MK-02. Six patients who discontinued MK-02 because of dryness felt so uncomfortable upon the return of rigidity and immobility that they resumed MK-02 in smaller dosage within two to five days and disregarded the small amount of dryness they encoun-

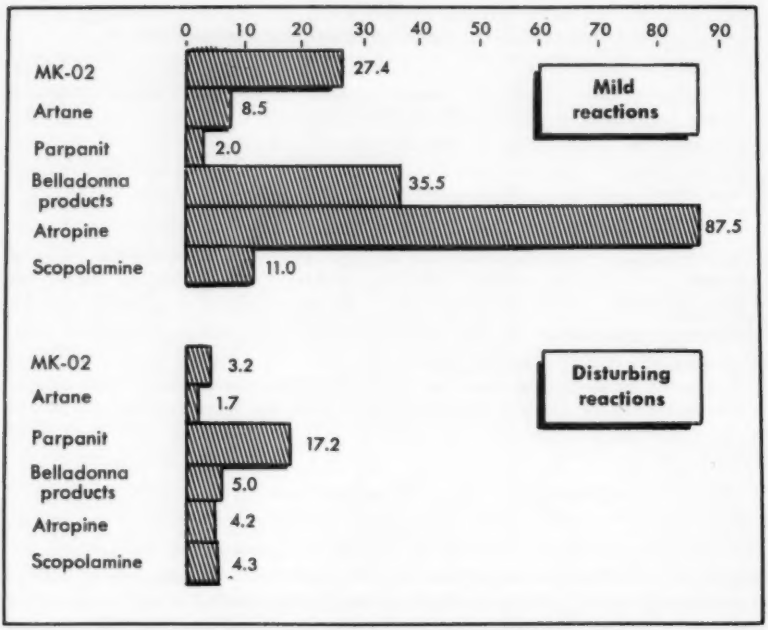


FIG. 1. Percentage of mild reactions (dryness of mouth and blurred vision) and disturbing reactions (dizziness, tachycardia, prostration, nausea and depression) among different drugs employed in the treatment of parkinsonism (based on table I.). The low figure of disturbing reactions with atropine is explained by the fact that this drug was employed only in postencephalitic cases, who possess tremendous tolerance for antiparkinson drugs.

tered. Blurred vision appeared among three of the 62 patients under observation. The only other side effects of any note were transient weakness, listlessness and depression. Patients experiencing these symptoms were given Artane in addition to MK-02 and had no further difficulties on this score.

It can be stated safely that not a single patient among the 62 followed to date suffered any dangerous ill effects from MK-02. Any side reactions that occurred such as dryness of the throat, tiredness, weakness or lassitude were either of transient nature, were tolerated, or disappeared within a day or two after cessation of treatment. MK-02 was tolerated equally well by arteriosclerotic, idiopathic and postencephalitic Parkinson patients. Five of the original 20 cases have continued on MK-02 for 10 to 12 months and eight for seven to nine months without any sign of deleterious effect. MK-02 does not affect the pulse or blood pressure and no complaints of tachycardia, flushing of the face or vertigo were noted. The drug apparently has minimal or no effects on the cardiac branch of the vagus. There was no evidence of

gastrointestinal difficulty. Urinalysis and blood counts done in a majority of the patients failed to reveal any abnormalities.

Table 1 is a compilation of various reactions among the 62 patients under treatment with MK-02. Comparisons are made with Artane, atropine, scopolamine, various forms of belladonna and Panparnit. This table is summarized graphically in figure 1.

DISCUSSION

It has been the experience of clinicians[10,11] who have done extensive work in the field, that no single drug can be expected to be beneficial in every case. The most suitable treatment or combination of treatments must depend upon the therapeutic requirements of the individual patient. It is especially so because we are dealing with different age groups, types of parkinsonism and tolerance in the patients, so that what may prove a blessing to the post-encephalitic patient may be a detriment to the arteriosclerotic patient. This and other factors determine the need for a wide assortment of useful drugs.[12] Thus, many patients tire of any remedy during the long siege of the illness and make repeated demands for changes in therapy. Again, some of the drugs lose their effects within a relatively short time and others in the course of years, because of increased tolerance in the patient or because of progression in the underlying pathology.

Another point to remember is that older patients are extremely sensitive to almost any form of therapy. When the dose of a drug is increased during efforts to compensate for diminishing returns, the side effects often prove so disturbing that they nullify all benefits derived from the drug and make it necessary either to discontinue the preparation, or to reduce the dose and add other preparations to the regimen. Therefore, some patients have to be given two or even three antiparkinson preparations at the same time, in addition to vitamins, tonics and physiotherapy, in order to bring them the greatest measure of relief and comfort. Furthermore, it is common experience that one drug is better for the control of rigidity, another for tremor, another for sialorrhea and still another as a cerebral stimulant. Admittedly, in the interests of scientific precision, we should like to conduct a survey with but one drug at a time. However, we cannot lose sight of the fact that, since we have no specific cure for the illness and from the nature of the pathology none is to be expected, it is the patient that matters rather than the drug or the experiment. Thus it is necessary to administer several drugs concomitantly to some of the patients.

It is an accepted fact that psychogenic factors render the precise evaluation of any drug impossible in this illness[13]. Some patients reject a drug, but upon shifting to another preparation they return to the original treatment. Others readily tire of any remedy and are so desperate for a cure that they absorb everything they read and hear and are in an endless search for something new. Some, on the other hand, are highly distrustful of new drugs,

because of fixed notions that they are being made subjects of experiment. Still other patients are forever studying the doctor to see what report will please him the most, whenever they are placed on a new remedy. In addition, some patients are unable to render intelligent reports on effects and side reactions. These and other uncontrolled variables seriously interfere with an exact evaluation of drugs in the treatment of parkinsonism[14] and explain why widely differing opinions are offered by investigators studying the same preparation.

It should be remembered that in parkinsonism the patient rather than the physician determines the therapy, because the length of the illness leads patients to shift and experiment with various drugs, until they find those that provide the greatest comfort and relief from symptoms. Thus it follows that drugs which possess some positive value to the patients never fail to find their true level of use in accordance with their merits.

SUMMARY

1. Due to the increasing number of cases, the long duration of illness, the imperfections in our current therapy and the changing tolerances, tastes and requirements of patients, there is a growing need for new remedies in the treatment of parkinsonism.

2. MK-02, a new synthetic combining the active radicles of atropine and Benadryl, has been found to be a valuable addition to the therapy of parkinsonism in a small series of 20 cases. Details of administration and dosage are provided. The drug has a powerful antispasmodic action, works peripherally and seems devoid of cerebral stimulating qualities. Hence in some cases it is used to best advantage in conjunction with Artane or other cerebral stimulant. It has a cumulative action which permits twice-a-day treatment to be effective and spares the patient the usual anxiety of having to watch for the hour of medication. It proved especially effective against rigidity, spasm, cramping of toes, contractures, sialorrhoea and severe tremor and was found helpful to 13 cases among the 20.

3. The findings with MK-02, while not conclusive, are nevertheless encouraging, especially because the compound appears to be harmless in clinical dosage. MK-02 is safe to employ in all forms of parkinsonism and it is recommended particularly for the control of rigidity, spasm and fixed facies in post-encephalitic patients and for severe tremor in arteriosclerotic patients. Pharmacologic studies prove that MK-02 has a large margin of therapeutic safety. It appears to be a valuable addition to the armamentarium of useful drugs for ment of parkinsonism.

CONCLUSIONS

1. A new synthetic preparation MK-02 offers great promise of usefulness in the control of rigidity, cramps, spasm, sialorrhoea and tremor in patients with parkinsonism. On the basis of results in a preliminary study with 20 cases, it appears that the preparation is practically non-toxic and is of value to patients in all groups of parkinsonism.

2. MK-02 is effective peripherally and is devoid of cerebral stimulation, hence is employed to best advantage when combined with Artane.

3. Further study of the compound is necessary, especially since it has cumulative qualities lasting three days and because proper regulation of the dose bears significantly upon the therapeutic effects and side reactions.

Expression of thanks is due to Merck & Co., for its liberal supply of MK-02 to meet the needs of our investigation, and to the physicians who assisted in this study.

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The first symptoms of this *insidious* disease is weakness and tremor, or the head, for instance, of the hand, etc. In about a year, the other hand, or a lower extremity, is affected, or the patient loses his balance in walking. Generally no *cause* can be assigned.

There is perpetual tremor, even when the part is supported: the head, the hand, the leg, are moved incessantly; reading and writing become impossible, and the patient cannot guide his hand to his mouth; at length he loses his balance, and there is a constant tendency to fall forwards, and, in order to avoid this, to run or move with a quicker pace, and on the toes.

At a later period the tremor continues during sleep even, augmenting until the patient awakes. There is increased weakness, the trunk is bent forwards, the upright position can no longer be supported. The articulation becomes indistinct, mastication and swallowing imperfect. The bowels are all along torpid, then obstinate, at last the urine and faeces are passed involuntarily. In the last stage of all there is slight delirium or lethargy.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases,* published in 1876.

Effect of Stimulation and Section of the Chorda Tympani Nerve

Samuel Rosen, M.D.

THE present study grew out of the use of the chorda tympani nerve as a new technique in the fenestration operation for otosclerosis. The chorda tympani was grasped with a jeweler's tweezers about three to five millimeters below the malleus. Traction upward pulled the chorda out of its bony canal. The chorda tympani nerve was then placed over the length of the artificially created fenestra in the bony horizontal semicircular canal. This technique was introduced in an attempt to protect the exposed membranous labyrinth from excessive postoperative labyrinthitis. Later on it was noted that certain patients with severe tinnitus, vertigo and deafness, whether associated with otosclerosis or not, could be relieved by a new technique which preserved the static labyrinth and cochlea. This procedure consisted of a single operation combining the fenestration, section of the chorda tympani nerve, and interruption of the tympanic plexus of nerves. Satisfactory results followed this procedure.[2]

Of interest in this connection is the work of Schneider[3] on a new theory of hearing which implicates the tympanic plexus and the chorda tympani nerve in tinnitus, vertigo and deafness. Fifteen patients suffering mostly from various combinations of severe tinnitus, vertigo, deafness, hyperacusis and diplacusis (Meniere's Disease) were operated on. These cases will be reported separately.

PROCEDURE

The simple operation was performed through an ear speculum in the external auditory canal and consisted in sectioning the easily accessible chorda tympani nerve in the tympanum. Nembutal and Demerol analgesia and local Novocain injection into the memberanous canal wall were used. Patients were sufficiently alert to respond adequately to questions and to report their sensations during the operation.

An incision is made through the skin over the bony canal wall from two o'clock to nine o'clock about five to seven millimeters external to the drum. The skin is separated as far as the drum. The drum is then lifted out of its sulcus and reflected upward upon itself like an apron, thus exposing the tym-

From the otolaryngological service, Mt. Sinai Hospital, New York City.

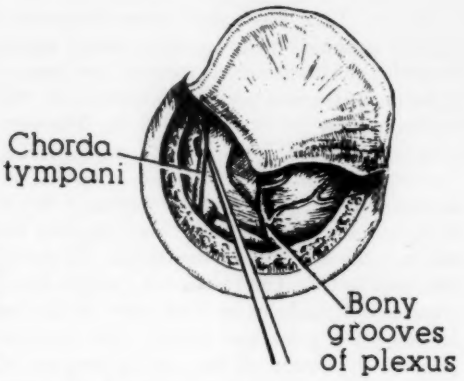

FIG. 1. Eardrum lifted out of its sulcus and reflected upward upon itself. The chorda tympani nerve can be seen in the grasp of the iris hook ready to be sectioned. The bony grooves of the tympanic plexus of nerves can be seen.

panic cavity. In half the cases the chorda tympani was visible at once for about four to six millimeters. In the rest, it was teased out into the tympanum from just behind the bony edge of the canal wall.

For stimulation a faradic type 120 cycle current was employed. The current characteristics found effective were 2 to 3 volts at 0.2 to 0.3 milliamperes. Long insulated electrodes were used.

RESULTS

Stimulation of intact chorda tympani: In all cases, the instant that the chorda was stimulated there was a violent contraction of all the homolateral facial muscles. In some of the patients severe pain deep in the ear and behind the auricle was experienced with each stimulation. The facial contraction and pain ceased the instant stimulation was stopped. Stimulation was repeated three to five times on each patient with the same result. Also, some patients reported sensations including loud tinnitus of varying pitch and character (roaring, hissing, buzzing, etc.) and rotatory vertigo with each stimulation. One patient reported momentary cessation of existing tinnitus with each stimulation. These reported sensations occurred only on the side stimulated. The sensations ceased just as soon as the stimulation was withdrawn. No autonomic changes in or about the ear were apparent.

Stimulation of sectioned chorda tympani: The chorda in the tympanum was then sectioned into two parts by engaging it and pulling it outward with a small iris hook (figure 1). The two separated ends were in turn stimulated independently. Stimulation of the central end (the portion running with the facial nerve to the geniculate ganglion) gave responses similar to those of the intact chorda tympani in over 80 per cent of the trials, whereas stimulation of the distal end (the portion running peripherally to the tongue) gave no facial contraction nor any sensation regarding tinnitus or vertigo. Stimulation of the malleus or bony canal wall similarly gave no facial contraction nor any tinnitus or vertigo.

Taste: Taste was tested before operation separately on both sides of the tongue anteriorly with a cotton wound applicator dipped in solutions made according to Börnstein[4] as follows; cane sugar, 40.0 grams per 100 cc., sodium chloride, 15.0 grams per 100 cc., citric acid, 10.0 grams per 100 cc., and quinine hydrochloride, 1.0 gram per 100 cc. The patient was instructed to keep the tongue protruded until he could compare taste on both sides of the tongue. No patient reported any sensation of taste at any time on stimulating the intact chorda or either portion of the sectioned chorda. In all cases following section of the chorda tympani there was complete loss of taste on the anterior two-thirds of the same side of the tongue. Eleven of the patients were not aware of this until tested. The rest noted a slight disturbance in taste. Pain and touch were tested similarly on both sides of the anterior two-thirds of the tongue by sharp pin prick and cotton. The sensations of pain and touch were unaffected by section of the chorda tympani, the response being prompt, accurate and equal on both sides of the tongue in direct proportion to the pressure of the pin prick or cotton swab.

Search of the available literature revealed no reference to facial contraction elicited by stimulation of the chorda tympani nerve. No reference was found to the subjective reports of tinnitus and vertigo on stimulation of the chorda tympani. These observations pose a number of questions about the pathways involved, and whether the chorda tympani participates in sonic and equilibratory sensations as well as taste. Some of these problems will be the subject of further investigations.

SUMMARY

1. Electrical stimulation of the intact chorda tympani nerve caused marked homolateral facial contraction in all cases and caused pain in and behind the ear in some cases.

2. Some patients reported tinnitus and vertigo on stimulating the chorda tympani nerve, but none of the patients reported taste.

3. Electrical stimulation of the central end of the sectioned chorda gave responses similar to those of the intact chorda in over 80 per cent of the trials.

4. Electrical stimulation of the distal end of the sectioned chorda tympani, malleus, and bony canal wall gave no facial contraction nor any subjective sensation.

5. Section of the chorda tympani was followed by complete loss of taste on the homolateral, anterior two-thirds of the tongue.

6. Sensations of pain and touch were unaffected by section of the chorda tympani.

I am indebted to Dr. William Bierman, attending physician in physical medicine, the Mount Sinai Hospital, for his cooperation in the performance of the electrical tests, and to Teca Corporation, New York, for their construction of the special apparatus employed in the performance of these tests.

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The senses are the smell, the sight, the hearing, the taste, and the touch; they convey to the mind all we know of the external world. Perception is derived from them. Volition is a subsequent mental act, and voluntary motion a frequent result. And thus the motions which result from sensation always *imply volition;* but as volition may exist without any previous sensation, the voluntary motions are frequently *spontaneous.* It is by this character that the motions which belong to the sentient and voluntary system are distinguished from those which belong to the excito-motory; these are never spontaneous; they are *always excited.* Even the motions of respiration, as far as they belong to this system, are excited motions, as I shall show immediately. Legallois, M. Flourens, Sir Charles Bell, are equally in error, I think, when they consider the medulla oblongata as the *source,* the *primum mobile,* of the respiratory motions; it is the *channel* through which the excitors act, and the organ which *combines* the different movements which constitute the acts of respiration; but the true source of these movements are certain excitor nerves,—the excitors of respiration—and principally branches of the pneumo-gastric, but also of the fifth and spinal nerves. Equally remote from the truth, I think, is the opinion of Dr. Philip and Mr. Mayo, that the acts of the respiration are entirely voluntary. This is, in fact, a mixed function, as all the acts of the excito-motory system may be; and although generally belonging to the excito-motory system, yet capable of being affected through the medium of volition.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases,* published in 1876.

Electroencephalographic Study of Patients With Tuberous Sclerosis

Willard W. Dickerson, M.D.
and C. David Hellman

Tuberous sclerosis (Bourneville's disease) is characterized by epilepsy, adenoma sebaceum and mental deficiency. Some subjects with the disease are reported to have retinal and visceral tumors and various other lesions involving the skin. Areas of decreased density and periosteal changes have been found in the bones of the hands and feet. Characteristic cranial calcifications have also been described. Not all of these signs appear in each patient but the first three are most common. In some instances the disease is known to show a familial trend.

Electroencephalographic studies on patients with the diagnosis of tuberous sclerosis are rare in the literature concerning this disease. Busse and Ebaugh[1] briefly mention tuberous sclerosis in their discussion of degenerative brain diseases and illustrate their paper with a sample of high voltage slow activity. O'Leary[2] mentions a case of tuberous sclerosis having focal abnormal findings. Liebert[3] stated that "electroencephalographic tracings on one of our cases did not show any evidence of discharges usually connected with tumor formation, but rather such potential differences as are usually seen in cases of idiopathic epilepsy." Paillas and Cain[4] give more detailed information on twin sisters with tuberous sclerosis. The electroencephalogram of one was "within normal limits prior to hyperventilation." No comment is made on the results of deep breathing or the recovery period. The other exhibited "high voltage waves on a baseline limited to 7.5."

Friedman[5] has reported a 20 month old girl with attacks of jerking of the extremities and unconsciousness. The patient had areas of depigmentation and hyperpigmentation of her body. An area of depigmentation was noted in the left fundus. Skull films showed calcification. Her electroencephalogram "revealed waves that were highly consistent with convulsive disorder." Goodfriend commented on the record and stated that "the electroencephalograms (on such patients) show nothing characteristic but are usually composed of markedly dysrhythmic waves and often show the type of abnormality which is exhibited by the present patient of high spike waves followed by slow high

From the Caro State Hospital for Epileptics, Caro, Michigan.

voltage waves. These may occur either focally or generally throughout the record."

Good and Garb[6] reported the electroencephalograph of a 20 year old patient with tuberous sclerosis as "a borderline normal record, which pattern is often seen in convulsive disorders in a quiescent interval." A second record five months later was reported as "essentially the same as noted in the previous examination, with the exceptions that there was a slightly greater incidence of 5 to 7 cycles per second waves bilaterally and on one occasion a short burst of high amplitude 3 cycle per second potentials appeared synchronously from both sides of the head. A mild degree of diffuse abnormal electrocortical activity was present over the entire cortex. No evidence of a localized lesion was noted. The pattern was suggestive of a convulsive disorder."

Constantine[7] included results of an electroencephalographic study in an account of a 10 year old, mentally deficient epileptic patient who had adenoma sebacum, cranial calcification and phakomata. "The record was reported abnormal and compatible with the diagnosis of tuberous sclerosis." Hoen, in discussing this paper, stated that "there were abnormal waves of average voltage and a slow rhythm, which are characteristic of neoplasms in general. The fact that the slow waves could be picked up over various parts of the cortex strengthened the feeling that the boy had numerous tumors in the brain."

TECHNIQUE

The recording technique was basically similar in all recordings and consisted of applying from eight to 18 scalp leads over standard areas by the collodion method. These included the bilateral frontal, premotor, motor, parietal, occipital, low-motor, anterior-temporal, low-temporal and posterior-temporal regions. In addition, "vector" leads were sometimes applied to the nose, vertex, mid-motor and occipital protuberance for use in a modified version of Bagchi and Basset's[8] technique. The recordings include scalp to scalp as well as scalp to ipsilateral or contralateral reference points on the ear lobes. Parallel reference point to scalp technique was also employed. The recordings were made in a darkened room with the patient in the supine position. The records usually lasted from 20 to 30 minutes on the eight lead studies and up to two hours with additional leads. Shorter records only were possible on some hyperactive patients. Few of the patients were hyperventilated, due to their inability to follow simple directions.

The earliest studies were made on a six channel, electric stylus machine writing on waxed paper. Later, all patients but one were re-studied on an eight channel ink-writing machine.

The patients examined included severely mentally retarded and combative patients who were not able to assist in the procedures. For this reason, many received a Seconal capsule (0.1 gm.) orally one hour before the preparation period. Some of the observations include sleep in varying stages. As the value of sleep studies and sequence of sleep patternings have been previously reported, no details of this aspect will be discussed. Although sleep observations have been reported as ideal for recording an epileptic patient,[9] the drug was intended primarily to obtain an artifact-free record.

CLINICAL MATERIAL

One to three completed studies were made on 29 patients having tuberous sclerosis. All patients but one (case 8) were institutionalized.

TABLE 1

SUMMARY OF ELECTROENCEPHALOGRAPHIC STUDIES OF PATIENTS WITH TUBEROUS SCLEROSIS

Case	*Sex*	*Birthdate*	*I.Q.*	*Test Dates*	*Summary of Electroencephalograms*
1. F. McW.	Female	4-13-1900	57	8-18-46, 10-7-46, 10-4-50	Mildly abnormal and slightly suggestive of brain damage and epilepsy.
2. M. McW.	Female	2-7-1938	Unknown	11-20-50	Focally and paroxysmally abnormal indicative of brain damage and epilepsy.
3. M. McW.	Male	11-8-1939	Unknown	11-20-50	Focally and paroxysmally abnormal indicative of brain damage and epilepsy.
4. J. C.	Male	11-3-1924	19	8-14-46, 10-8-46, 10-3-50	Normal to mildly abnormal, slightly indicative of brain damage and epilepsy.
5. T. T.	Male	7-2-1939	45	9-19-46, 10-30-50	Paroxysmal abnormal to mildly abnormal. Indicative of organic damage and epilepsy.
6. P. T.	Female	5-16-1943	23	11-2-50	Focally and paroxysmally abnormal indicative of brain damage and epilepsy.
7. S. Y.	Female	8-3-1948	Unknown	9-12-49, 10-16-50	Organic damage and paroxysmal episodes. Focal signs present. "Epileptoid" pattern.
8. M. Y.	Female	4-17-1942	Unknown	9-3-49	Borderline abnormal, suggestive of non-localized brain damage.
9. A. P.	Male	5-22-1901	97	8-20-46, 10-7-46, 9-8-50	Questionably normal to borderline. Mild, localized brain damage.
10. I. Q.	Female	3-3-1928	Unknown	8-20-46	Abnormal (fast), non-focal, epilepsy.
11. H. A.	Female	5-8-1927	3	8-20-46	Abnormal (fast) with focal brain damage and indicative of grand mal epilepsy.
12. R. S.	Female	8-1925 (?)	4	8-21-46, 10-10-50	Paroxysmal and focal abnormal (fast). Organic brain damage and grand mal.
13. J. O.	Female	11-27-1912	35	8-21-46, 10-11-50	Focal abnormal, brain damage. Petit mal and grand mal epilepsy.
14. J. H.	Female	12-4-1918	6	8-21-46, 10-17-50	Paroxysmal and focally slow to abnormal slow. Brain damage and epilepsy.
15. D. P.	Female	5-24-1924	6	8-16-46, 10-12-50	Abnormal slow, suggestive focus. Diffuse brain damage.
16. H. R.	Male	7-5-1925	7	8-14-46, 10-9-50	Paroxysmal and focally abnormal. Generalized brain damage, epilepsy.
17. M. W.	Male	3-8-1938	29	8-14-46, 8-22-46, 10-10-50	Abnormal slow, paroxysmally slow or borderline with suggestive focus.
18. R. H.	Female	12-17-1925	41	10-7-48, 12-7-48, 10-6-50	Paroxysmally and focally abnormal. Petit mal and grand mal epilepsy.

TABLE 1 —*(Continued)*

Case	*Sex*	*Birthdate*	*I.Q.*	*Test Dates*	*Summary of Electroencephalograms*
19. H. B.	Male	8-16-1922	Unknown	11-3-48, 12-7-48	Normal, awake and asleep.
20. J. F.	Male	2-20-1939	7	10-10-50	Borderline, suggestive focal damage.
21. R. R.	Female	7-30-1930	2	10-1-46, 10-30-50	Paroxysmally and focally abnormal. Generalized brain damage and epilepsy.
22. F. D.	Male	9-5-1924	69	8-16-46, 10-7-46, 9-10-50	Paroxysmal abnormal, abnormal slow and borderline. Suggestive focal brain damage.
23. S. M.	Female	6-5-1929	2	8-15-46, 10-12-50	Paroxysmally and abnormal slow. Diffuse brain damage and mixed type of epilepsy.
24. G. L.	Male	8-31-1936	Unknown	8-15-46, 10-11-50	Paroxysmal abnormal with multiple foci. Brain damage and epilepsy.
25. F. D.	Female	10-24-1906	6	8-20-46, 10-11-50	Borderline abnormal. Suggestive brain damage.
26. F. T.	Female	4-27-1921	47	8-15-46, 10-8-46, 10-19-50	Abnormal slow with multiple foci. Pronounced "deterioration" effect.
27. Y. S.	Female	7-28-1931	Unknown	8-13-46, 10-3-46, 10-10-50	Abnormal slow and paroxysmal episodes. Focal brain damage and mixed epilepsy.
28. J. H.	Female	5-9-1933	46	12-1-47, 5-2-50	Abnormal with focal brain damage. Later improved. Suggestive epileptic patterns.
29. C. G.	Male	1926	Unknown	9-29-50	Paroxysmal and focal abnormal. Organic brain damage and epilepsy.

TABLE 2

SUMMARY OF ELECTROENCEPHALOGRAPHIC RESULTS OF RELATIVES RECORDED WITHOUT TUBEROUS SCLEROSIS

Case	*Sex*	*Birthdate*	*I.Q.*	*Test Dates*	*Summary of Electroencephalograms*
30. D. McW.	Female	1934	Unknown	11-20-50	Abnormal slow and focal brain damage.
31. F. B.	Female	12-15-1937	Unknown	11-20-50	Abnormal slow, non-focal. Brain damage.
32. E. T.	Female	1916	Unknown	9-19-46	Normal.
33. G. T.	Male	10-20-1912	Unknown	11-11-50	Normal.
34. M. Y.	Female	1911	Unknown	9-3-49	Within normal limits.
35. L. Y.	Male	1904	Unknown	9-3-49	Within normal limits.

It was possible to make one record of six blood relatives of various patients in this study. Case 1 is the mother of cases 2, 3 and 30. Case 30 is a feeble-minded daughter who does not have tuberous sclerosis. Case 31 is a paternal second cousin of case 1, who is also feeble-minded but does not have tuberous sclerosis. Case 1 is also the maternal aunt of case 4. Case 5 and 6 are the son and daughter of cases 32 and 33. The father (case 33) had convulsions in his teens. Cases 7 and 8 are the daughters of cases 34 and 35. The mother (case 34) of these girls has adenoma sebaceum, but has never had a convulsion. Copies of electroencephalographic reports have been obtained on the feeble-minded sister and brother of case 4. The sister is feeble-minded, epileptic and has adenoma sebaceum and phacomata. Her electroencephalogram was reported as "borderline character having some definite normal features in addition to quite a few atypical and abnormal features some of them being of an epileptoid form. The whole record is suggestive but not diagnostic of a convulsive disorder. No localizing sign." The feeble-minded brother who does not have tuberous sclerosis is reported to have "moody spells." His record was "definitely abnormal and is very highly suggestive of an epileptic brain. No remarkable localizing sign in the cortex for any gross lesions."

RESULTS

A total of 58 electroencephalograms were completed from the 29 patients in our studies and are summarized in table 1. The results are classified in five groups: (1) Normal studies, awake and asleep. (2) Borderline or mildly abnormal records, including those with questionable focal signs or mild evidence of organic damage or convulsive disorders of a non-specific type. (3) Abnormal recordings of slow, fast or mixed fast and slow, without paroxysmal episodes including focal or non-focal features. These records were considered to be primarily indicative of diffuse brain damage. (4) Paroxysmally abnormal studies which do not show any evidence of brain damage. (5) Paroxysmally and focally abnormal records which are equally evident of convulsive disorders and localized brain damage.

It was found that five records or approximately 9 per cent were in group 1. Thirteen records or approximately 22 per cent were in group 2. Twenty-two records or approximately 37 per cent were in group 3. One record or approximately 2 per cent was in group 4, while 17 records or approximately 30 per cent were in group 5.

The results include the localization studies made on six patients. Attempts were made to detect areas of greatest density seen in the roentgenograms of the skull but it was not possible to localize or to correlate types of patterns with these areas. The records of four of the patients who had localization studies did not reveal any more abnormality than was seen during the routine observation. One patient had shown some improvement in cortical activity with a 12 lead study, and continued to show improvement at the time of a full localization recording. One patient's localization recording showed a decline in cortical stability when compared to the routine recording.

One patient, case 18, had additional leads applied over the bilateral temporal lobe areas. In this case, a sleep study showed negative spikes over a part of the bilateral low-motor to anterior-temporal lobes which were similar to the spikes reported by Gibbs and Gibbs[10] from patients having psychomotor epilepsy. This patient showed more paroxysmal three-per-second wave and spike discharges correlated with clinical petit mal attacks than any other patient studied.

Twenty-one records of groups 3 and 5 contained clear-cut focal abnormalities. These consisted of marked voltage suppression, sharp spikes or a consistent asynchrony when the focal areas were compared with the homologous areas. Seventeen records from groups 2, 3 and 5 contained questionable focal features of a slight asymmetry or asynchrony or poorly formed spike activity. Some patients' records did not show consistent focal findings. The focal features were not always confined to one hemisphere or an area in a hemisphere, often being bilateral or diffuse. There were recordings which showed more than one type of a focal abnormality, but the most common abnormal features were high voltage slow waves, sharp waves or areas of voltage suppression. Fast recordings were definitely in the minority. Several patients exhibited a "stereotyped" six cycle rhythm of medium voltage lacking a modulation effect, which was felt to be associated with electrodynamic deterioration.

The patients did not always demonstrate identical patterns at the time of repeat studies. In 22 patients, 12 had patterns which did not materially change from study to study. The changes of patterns were usually minor in type, although some patients did not show paroxysmal activity upon repeat examination. However, the basic rhythm continued to show features which were definitely indicative of brain damage. Only one patient showed a marked swing from abnormally slow to abnormally fast frequencies. Two showed a decline in cortical stability upon repeat examinations. Seven patients' records showed a slight improvement in pattern while only one patient's second record was worse than the initial study. The only patient (case 10) in the group with consistently normal findings is on parole and seizure free, according to last reports. This man, while not a classical case of tuberous sclerosis, presents features of this syndrome combined with those of Sturge-Weber disease.

Table 2 is a summary of the electroencephalographic studies of the six relatives of patients with tuberous sclerosis. The results of the six tests show 33.5 per cent definitely abnormal findings and 66.5 per cent normal results. These figures are similar to those previously given by Robinson[11] who reported a larger group of relatives of institutionalized epileptics. It is not known if his patient or relative group included subjects with tuberous sclerosis.

DISCUSSION

Good and Garb[6] have stated that the "electroencephalogram may be a useful diagnostic aid in discovering *formes frustes* of tuberous sclerosis in members or relatives of patients with epiloia, who show no eivdence of men-

tal, neurologic or cutaneous changes." They also say, "the opinion is advanced that perhaps by further study of groups of patients with tuberous sclerosis, types of patterns may be obtained which would differentiate this disease from other types of convulsive disorders, just as symptomatic epilepsy can be frequently differentiated from idiopathic epilepsy."

No specific or common pattern was found in the recording in this study. It was noted that the percentage of normal records was less than in 3,000 recordings of institutionalized epileptics. Focal findings were common, but these were not specific in nature. This does not agree with Constantine's[7] conclusion that a record can be "compatible with a diagnosis of tuberous sclerosis." No single feature was found which would distinguish the results of this study from records of other patients who have epilepsy, mental deficiency and other forms of organic brain disease.

Good and Garb[6] have shown the strong familial tendency for abnormal patterns, such as was found in case 1 of the present study and her three feeble-minded children, two of whom have tuberous sclerosis. It is likely that the third child may develop seizures at some future date, in view of the definitely abnormal record which was equally indicative of convulsive disorders and brain damage.

SUMMARY

Electroencephalographic studies of patients with the diagnosis of tuberous sclerosis show a higher percentage of abnormal records than do institutionalized epileptics who do not have this disease.

No specific pattern was found which could be considered diagnostic of tuberous sclerosis.

It was not possible to localize the tuberose nodules in the brain characteristic of the disease.

The recordings of blood relatives of patients with tuberous sclerosis were similar to the results published previously by Robinson on relatives of epileptics without tuberous sclerosis.

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Neurologic Manifestations Following Spinal Anesthesia

Jost J. Michelsen, M.D.

THERE are numerous reports on the subject of neurologic complications following spinal anesthesia.[1–6] Manifestations vary greatly, with headaches, nausea and vomiting, often associated with neck rigidity, rather common. Next in frequency is urinary retention. Among the more serious and fortunately rare neurologic entities due to the noxious effect of anesthetics are spinal arachnoiditis,[4] cauda equina involvement[7] and myelitis.[8,9]

The question as to why complications develop in some patients but not in the majority of them has not been clearly answered. In some instances the causal relationship is obvious. Direct trauma will occasionally produce what could be designated as radiculitis. There have been sporadic infections of the epidural and subarachnoid space. The principal etiologic factor and/or mechanism of the damaging action of the anesthetic drugs are rather obscure. It seems impossible to predict with reasonable certainty whether or not the spinal anesthetic will be well tolerated by a given patient.

Lundy[10] suggested that many spinal anesthesia accidents are due to factors other than the primary action of the anesthetic agent and that the spinal cord had probably been previously diseased if there is paralysis following the use of ordinary doses of the anesthetic. Michelsen[11] emphasized the importance of a good history, neurologic examination and occasional cerebrospinal fluid analysis before the anesthetic is given, in order to prevent serious neural damage. He also has pointed out that the choice of anesthesia should be made with great caution in patients with syphilis, recent furunculosis, rheumatoid arthritis, tuberculosis, etc.

Wilson and associates[6] cited a case in which the first manifestations of multiple sclerosis occurred a few days following an operation for which spinal anesthesia has been given. A second patient, who developed transverse myelitis in the mid-thoracic area, was found to have an intramedullary tuberculoma. They emphasized that spinal anesthesia should not be used in patients with congenital anomalies of the nervous system, with known virus infec-

From the department of neurosurgery, Massachusetts General Hospital, and the department of neurology, Harvard Medical School, Boston.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1951.

tions, or with a history of delayed return of motor function or severe paresthesiae following a previous spinal anesthesia. They also cautioned against its use when there is severe inanition and vitamin deficiency. Nicholson and Eversole[12] described two cases in which neurologic manifestations of preexisting cord lesions were precipitated.

One of the four cases reported here was first described 19 years ago.[13] The other three patients have been observed within a period of two years. The older case is included because it is very similar to one of the recent observations.

CASE REPORTS

Case 1. A woman aged 32 was admitted to the hospital complaining of weakness in both legs. Three years previously she had had two abdominal operations. One for a stomach ulcer was performed under general anesthesia; the postoperative recovery was uncomplicated. The second, for an ovarian tumor, was done under spinal anesthesia; twelve hours later she developed hypersensitivity of both legs, with severe pains involving the entire right leg and the heel and toes of the left foot. There was paralysis of the right leg except for some action at the hip joint; on the left, movements of the toes were limited. Bladder and bowels did not function. Motor and sensory functions improved gradually and she was able to walk after six weeks. After about a year she returned to her previous occupation as a nursery teacher. The extent of neurologic deficit could not be ascertained at that time. She continued to have difficulties with her urinary bladder. Three years later she began to have pains and paresthesias in the left heel and the anteromedial right thigh. The right leg became stiff and both legs gradually became weak. On examination she showed complete paralysis of both lower legs and feet; patellar and ankle clonus bilaterally, more so on the right; bilateral pyramidal reflexes and sensory loss, more pronounced on the right, with a level approximately at the groin. Spinal fluid contained increased protein, and myelographic studies disclosed a partial block with an expanding lesion opposite the twelfth thoracic vertebra. This lesion was found to be an epidermoid tumor.

Case 2. A woman aged 31 was admitted to the hospital with the chief complaint of pain in the low back and left lower extremity. Three years prior to hospital admission she had had an abdominal operation under spinal anesthesia. Following this operation she was paralyzed from the waist down on the left side with marked impairment of bladder and bowel function. Her condition gradually improved, but the left leg remained weak and she continued to experience constant numbness of the anterior surface of the toes, foot and lower leg, and intermittent episodes of pains and cramps of the calf muscles. Later she developed pains in the low back, left buttock and posterior thigh which were aggravated by bending, coughing and lifting. The numbness in the left leg increased and spread to the saddle area. Urinary difficulties progressed. On examination she showed marked weakness of the muscles of the left lower leg and foot, sensory disturbances over the left lower leg, and dissociation of reflexes. Roentgenograms revealed a spina bifida occulta of the sacrum and incomplete fusion of the lamina of the fifth lumbar vertebra. There was an incomplete block on spinal puncture fluid studies with a total protein of 500 mg. Pantopaque myelography showed a block at the level of the fourth lumbar interspace. Operation disclosed an epidermoid tumor of the cauda equina.

Case 3. A woman aged 20 noted discomfort in the posterior cervical region, both shoulders and arms, and subsequently in both hands, four months prior to hospital admission. A diagnosis of bursitis was made. Several teeth were removed, with some relief for about two months when her symptoms reappeared. Bladder disturbances developed, and two days later, sharp, knife-like pains in the abdomen led to an appendectomy. Before

introducing the spinal anesthetic, the anesthetist observed that the spinal fluid was xanthochromic. Following the operation the patient developed paresthesias in both lower legs. A few days later her legs would not support her when she attempted to walk. Neurologically, she had marked generalized weakness of both legs and also of the arms, with an upper level at the seventh myotome. Deep reflexes were increased. Sensation was disturbed, the loss of pain and temperature sense being more marked on the right side. There was a partial manometric block on lumbar puncture; the spinal fluid protein was 250 mg. Myelographic studies revealed an expanding lesion at the C6-C7 level. An intramedullary ependymoma was found at operation.

Case 4. A woman aged 32 complained of pain in the left upper quadrant, radiating to the left back. Three months prior to admission she had been delivered normally, but one month prior to delivery she had had hemoptosis; she had several uterine hemorrhages following her discharge from the hospital. A mass was noted in the left upper quadrant and an abdominal operation was performed under spinal anesthesia. The operative findings were consistent with a diagnosis of pancreatic cyst. During the postoperative recovery the patient had incontinence of urine and feces. There were sensory disturbances from the umbilicus down to the feet. On the seventh postoperative day lack of motion was noted in both lower extremities. On the twelfth postoperative day the patient was found to have paraplegia with loss of all sensation below the level of the umbilicus. The spinal fluid was xanthochromic, with a total protein of 160 mg. There was a complete block on jugular compression, and myelographic study showed a block opposite the eleventh dorsal vertebra. At operation the patient was found to have a metastatic choreoepithelioma.

COMMENT

These four case histories were similar in many ways. At the time of injection of the anesthetic an intraspinal space-taking lesion was present. This was quite obvious in cases 3 and 4. The epidermoid tumors found in cases 1 and 2 were undoubtedly present three years prior to their removal, since the rate of growth of this type of lesion is known to be extremely slow.

In all four instances the neurologic manifestations occurred soon after the operative procedure for which spinal anesthetic was used. The anesthetic agent was introduced in the usual amounts and solutions by anesthetists of experience.

Other factors were variable. There was recovery, although incomplete, in cases 1 and 2 and none in cases 3 and 4. Complete block of the cerebrospinal fluid was found in one case, a partial block only in the other three. In case 2 the site of obstruction was below the interspace at which the spinal anesthetic was injected. In the other cases the lesion was above the level of injection.

A review of the various complications caused by spinal anesthesia indicates that one single factor cannot account for the widely divergent manifestations. In the search for injurious agents considerable evidence has been accumulated that a chemotoxic effect of the anesthetic drugs is an important factor. It has been observed that the nerve damage more often is greatest where the concentration of the drug is the highest, that is on the nerve roots of the cauda equina. However, why the concentration of the drug should vary from one case to the other under ordinary circumstances so that neurologic complications are produced, is not known.

In the present patients with tumors of the spinal cord, which as a rule interfere with the dynamics of the cerebrospinal fluid, lack of diffusion of the anesthetic on a mechanical basis would seem, at first glance, to be a plausible explanation. Yet, the dynamic block was incomplete in three cases at the time of hospital admission and presumably absent in cases 1 and 2 at the time the anesthetic was given.

Since the total protein of the cerebrospinal fluid was elevated in all four cases, the question arises whether diffusion rate, local concentration, and/or toxicity of the drug are affected by an elevated total protein concentration. Nicholson and Eversole[12] have stated that an elevated total protein should make one cautious with regard to the choice of spinal anesthesia. Further studies in this direction both in the laboratory and clinic are warranted.

If there were a relationship between spinal fluid protein elevation and toxicity of the anesthetic drugs, determination of the total protein prior to instillation of the anesthetic ought to become a routine procedure. It would correspond to heart, chest and urine examination in preparation of patients for inhalation anesthesia. Perhaps estimation of the protein content by rapid test would suffice. Since bleeding, which occasionally occurs during the tap, increases the protein content of the spinal fluid, it may well be a definite contraindication to the introduction of the anesthetic. Needless to say, a spinal anesthetic should never be injected in the presence of a dynamic cerebrospinal fluid block, because it interferes with the proper diffusion of the drug.

Spinal anesthesia was definitely contraindicated in cases 3 and 4. The discoloration of the cerebrospinal fluid in the former was observed, but its significance not recognized. In case 4 a complete dynamic block could have been discovered, but no manometric measurements were carried out. This omission, not particularly serious in accordance with present practices, also brings to mind the pre-anesthetic examination of the patient. When Bier[14] began to use spinal anesthesia some 50 years ago, diagnosis and treatment of intraspinal conditions were in their infancy. New clinical tools made diagnosis more precise. The technique of spinal anesthesia, however, has changed very little. Undoubtedly, with the firm establishment of anesthesia as a specialty, the more recent knowledge of cerebrospinal fluid abnormalities and its chemistry, cytology and dynamics will be more often applied in the management of spinal anesthesia. In the meantime, it is proposed that determination of the dynamics form an essential part of each cerebrospinal fluid examination. Such an examination will prevent accidents associated with preexisting intraspinal pathology of the obstructing type. A certain number of patients, even if small, brought to the operating room under a mistaken diagnosis—most frequently acute abdominal visceral disease—will be eliminated as candidates for spinal anesthesia. Whether or not increased intracranial pressure is a contraindication to the use of spinal anesthesia remains to be seen. In other instances, probably quite frequently, proper testing of the dynamics should help with the accurate placement of the needle, thus avoiding

subdural injection of the anesthetic or lateral deviation of the needle with root impingement.

Cytologic analysis of the cerebrospinal fluid prior to the spinal anesthesia might well be another important source of information.

Whether or not a more thorough physical and neurologic examination in cases 1 and 2 would have prevented the serious disabling postoperative complications is difficult to decide. It is a fact, however, that a large number of patients who are to receive spinal anesthesia have not even had their reflexes tested or pupils examined before they are sent to the operating room. Histories, past and recent, are sketchy. It is strange to see—and utterly tragic after an accident has happened—how readily the choice of spinal anesthesia is made by men who are not familiar with the basic principles of neurology, chiefly the pathophysiology and clinical lesions of the spinal cord.

Spinal anesthesia is very popular among anesthetists, particularly in the medium-sized and smaller hospitals. Its simplicity is always stressed. One must emphasize its dangers when given blindly. Spinal anesthesia must become at least as safe as it is simple.

SUMMARY

The neurologic manifestations following spinal anesthesia in four cases of intraspinal tumor are described. The possible mechanisms of the damaging action of the anesthetic are discussed. Measures to eliminate some of the spinal anesthesia complications are outlined.

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Environmental Studies in Multiple Sclerosis

Gabriel Steiner, M.D.

ENVIRONMENTAL studies in multiple sclerosis have been very much neglected. Recent mortality and morbidity statistics[1,2] show that there is a definite geographic difference in the occurrence of this disease.

The present environmental studies are limited to the state of Michigan. Five hundred cases were collected. About one-third came from the Multiple Sclerosis Center in Detroit Memorial Hospital. The other two-thirds were submitted by physicians who were asked about cases under their care during the last five years. Questionnaires were sent out to each patient. Only cases with well established diagnoses were accepted. Over 70 per cent of the cases were diagnosed at one time or another in one or more reliable neurologic departments (Mayo Clinic, Rochester, Minnesota; University Hospital, Ann Arbor; and Henry Ford Hospital, Detroit).

The fact that this material of 500 cases comes from two sources, one group examined and evaluated clinically in the Multiple Sclerosis Center and the other group obtained from questionnaire surveys of medical sources is of importance. The results are the same in both groups. With a population of 6,000,000, a total of about 2500 cases of multiple sclerosis might be expected in Michigan. This figure certainly represents a very crude estimate. Kurland's[2] statistics (multiple sclerosis three and one-half times as prevalent in Winnipeg as in New Orleans; Winnipeg 42 per 100,000 population, New Orleans 12 per 100,000) applied to Michigan would give a total of 2500 cases. These 500 cases would represent about one-fifth of the total number of multiple sclerosis cases in Michigan.

Questions were asked about birthdates, birthplaces, marriage dates, children, residences, vacations, farm contacts, occupations, occupations of fathers, accidents, hobbies, sports, pet animals, diseases of pet animals, insect bites, handling natural manure, and same or similar cases in the family, in neighbors or friends and other acquaintances. Statistical figures are not yet complete in so far as only 16 counties out of a total of 83 in the state were investigated.

From the department of neuropathology, Wayne University, Detroit, Michigan.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1951.

A few definite results, however, have been obtained.

1. A difference was found in various regions of the state. Places with high incidence of multiple sclerosis are Marquette (17,000 population), which had 21 cases of multiple sclerosis or a ratio of 124 to 100,000 population; Gladstone (4 cases in 4900 population); Iron Mountain (10 cases); Ironwood (5 cases); Lansing (18 cases) and Detroit. There were rural districts in which multiple sclerosis was more common than in others.

2. Intrafamilial cases. In places where multiple sclerosis is more common, there are often more cases in one household. In the 500 cases studied, there were 14 families in which there were more than one case of multiple sclerosis, totaling 28 cases; that is, 2.8 per cent familial occurrences or 5.6 per cent familial cases. Kolb found four occurrences among 199 families, about 2 per cent, and Sällström in Sweden found 17 cases among 1015, or about 1.67 per cent. The household cases in this survey were found in Detroit, Lansing, Marquette, Menominee, and in three rural communities in close vicinity. Of these 28 cases there were 20 females and eight males. Seven times multiple sclerosis was found in two sisters, twice in two brothers, once in one brother and one sister, twice in father and daughter, and once each in mother and daughter and mother and son. These figures show that in these households females are more exposed to the outside source of the disease than males and and that in families, combinations of multiple among siblings are two and one-half times more common than paternal-filial combinations. Apparently sisters and/or brothers are more exposed to the outside source of multiple sclerosis than parents and their sons or daughters.

It seems worthwhile to note that all of the familial cases shared the same household. In one case of two brothers and one case of two sisters the patients shared the same beds for some time before the onset of the disease. Of interest also is the presence of pet animals, dogs and cats, in the same household. Relatively often, these animals were infested with fleas. As to the occupations of the fathers, there seem to be some preferences: farming, gardening and greenhouse work, five times; building industry (lumberman, carpenter, contractor), five times; maintenance of estates (supervisor, janitor), three times; and teaching, three times. In one of the familial cases (father and daughter) the father had a work shop in the basement of his home.

3. If there is an environmental extrahuman source in our material, other non-familial contact cases should be found also. Of special interest is the case of a girl with multiple sclerosis of two months' duration which was verified by necropsy. In the home of this girl there was a boarder, a female nurse who took care of a chronic female case of multiple sclerosis in another part of the city. The girl was very fond of cats. At the time of death of this patient the cat was no longer available because it had to be removed from the home and sacrificed, the reason given was that the cat was flea-ridden.

4. If there is an environmental factor, the occupations of cases of multiple sclerosis may be of interest. In 500 cases of multiple sclerosis collected up

to the present, 34 teachers with multiple sclerosis were found. Twenty-five of these teachers were born and teaching in Michigan before the onset of their disease. It is interesting to note that the disease was found among elementary school and kindergarten teachers 24 times and among high school teachers only seven times. Also interesting is the high frequency of pet animals belonging to teachers. Cases of multiple sclerosis among non-teaching personnel in schools were found only three times (janitor; nun in a parochial school, working in the kitchen of this school; and a public health nurse).

These are some of the statistical facts. What are the conclusions?

1. There is no man to man transfer. There is no transovarian passage.

2. A *particular* environmental *extrahuman* reservoir of the disease agent is highly probable.

3. This extrahuman reservoir and its accumulation in the environment of certain groups, namely those sharing the same household or the same special occupation is responsible for the higher incidence in household groups (families) and among teachers, especially kindergarten and elementary school teachers, and moreso in rural areas.

4. In the same household siblings are more exposed to the extrahuman source than in the paternal-filial combination.

5. Dogs or cats may be suspected as reservoirs of the agent. However, the popularity of dogs as pets in the general population renders a statistical evaluation of this factor extremely difficult. Other investigations have been inaugurated.

6. Insect vectors as links in the chain of transmission may be significant or not; the chronicity of the disease and damaged memories in the later stages of the disease make the evaluation of this factor very difficult.

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The subject of the diagnosis of diseases of the brain certainly transcends in complexity, and perhaps exceeds in interest, all other problems in practical medicine. In nerve-elements the involution of energy reaches the highest degree known to us, and in the chief organ of the nervous system these elements vast in number, various in character, are arranged in what seems to us extreme complexity.

—Sir William R. Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Neurology

Clinical Pathologic Conference

From the Indiana University Medical Center

Presented by Alexander T. Ross, M.D., Robert F. Heimburger, M.D. and Orville T. Bailey, M.D.

PRESENTATION OF CASE

A 22 year old woman was referred to the Indiana University Medical Center because of paralysis of the right arm and leg and increasingly severe headaches. Owing to the patient's mental status, the history was obtained from a relative.

The patient had developed slowly as an infant, sitting up and walking later than her brothers and sisters. She was considered a normal child by her parents. When she went to school, progress was very slow and school authorities classified the patient as mentally defective. At 16 years of age she left school, having completed the work of the third grade. Her mental difficulty seemed to be increasing and it was noted that she was developing a tendency to stumble and fall frequently. Two years later, paralysis developed in the right arm and leg. How long the paralysis continued could not be determined, but it was present on admission to the hospital at the age of 22.

At 19, occasional episodes appeared which consisted of momentary loss of consciousness and sudden hyperextension of the neck. These were not preceded by an aura and incontinence did not occur. The frequency of the attacks increased; at the time of admission they occurred two or three times a week. Three months before coming to the hospital, the patient had without warning a more severe convulsion with protrusion of the tongue, hyperextension of the neck and incontinence, followed in about half an hour by vomiting of dark brown material. She was comatose for four or five hours after the episode. There were two more severe attacks, neither so severe as the first. From the time of the first major seizure until admission, the patient fell very frequently and required constant supervision. Headaches, which first made their appearance 10 years before admission, became much more troublesome for the two months preceding hospitalization. Phenobarbital administration apparently diminished the severity of convulsions but did not relieve the headaches.

The patient had had the usual childhood diseases with no sequelae and a tonsillectomy and adenoidectomy at 10 years of age. Menarche occurred at 14. The menstrual periods were regular until the age of 17, after which she menstruated every four or five months for two days. The patient's father died of a pulmonary condition, the nature of which could not be determined. Her mother was living, but was bedfast for reasons which the informant could not supply. No data could be secured on the health of the mother during pregnancy. One sister and three brothers were normal.

FIG. 1. Lateral view of the ventricular system showing filling of the third ventricle with the two air-filled spaces discussed in the text.

On *physical examination*, the patient was a rather obese young woman with a child-like facial expression, prominent frontal bosses and widely set eyes. The blood pressure was 126 mg. Hg. systolic; 72 mg. Hg. diastolic. Respirations were deep and regular at 16 per minute. The pulse rate was 56 per minute. No additional abnormalities were found on general physical examination.

On *neurological examination*, the patient seemed mentally dull and had a poor memory for past and recent events. However, she was oriented as to time, place and person and cooperated within the limits of her mental status. Her speech was distinct and her vocabulary satisfactory for a person who had completed the third grade in school. The patient was cheerful to a degree almost inconsistent with her difficulties. She was right-handed. Tests of the cranial nerves were normal except for those of the optic nerve. Visual acuity was 20/50 in the right eye and 20/200 in the left. The ocular fundi showed 2 diopters of papilledema with severe engorgement of the retinal veins, but no hemorrhages or exudates were present. There was horizontal nystagmus on right lateral gaze. The pupils were dilated but reacted promptly to light and in accommodation. Sensation and motor power were normal in the trunk and extremities. The patient found it difficult to stand and, when urged against her wishes to walk, it was with an ataxic, wide-based gait. She had a tendency to fall toward the left and Romberg's sign was positive. There was moderate dysmetria of the left hand. The tendon reflexes were active, being slightly increased on the right side. The abdominal reflexes were absent. Attempts to elicit Hoffman's and Babinski's signs led to normal responses.

Laboratory examinations of urine and blood (including serology) yielded values within normal limits, except for the blood sugar, which was 145 mg. per 100 cc.

Roentgenograms showed an increase in the digital markings of the inner table of the skull with moderate separation of the cranial sutures. The sella turcica was enlarged. There was destruction of the anterior and posterior clinoid processes, as well as roughening and irregularity of the clivus. The lesser wing of the sphenoid on both sides was more radiolucent than normal, and the superior and inferior orbital fissures were partially destroyed.

Ten days after admission, ventriculography was carried out through a right parietal burr hole (figure 1). Three hundred cc. of fluid were removed and replaced with air. Roentgenograms after this procedure showed tremendous dilatation of the lateral ventricles without apparent shift. The third ventricle was also dilated, extending posteriorly as a smooth, rounded cavity to the region of the tentorial incisura. At this point, there was a constriction which was interpreted as a dilated aqueduct of Sylvius. Below the constriction, there was another smoothly rounded cavity, regarded as a dilated fourth ventricle. During the manipulation incident to ventriculography, some of the air escaped into the cisterna magna.

Clinical course: Because the roentgenograms failed to demonstrate a block of the cerebrospinal fluid or a tumor, no operative procedure was undertaken. The patient had no trouble immediately after the ventriculo-

gram, but on the following afternoon she became drowsy and vomited. The pulse was 80 per minute and the blood pressure 120/90 mg. Hg. During the evening, the pulse grew much slower and the blood pressure was elevated. The patient became comatose. Roentgenograms at this time showed no absorption of air or change in its distribution. There was no evidence of air in the subarachnoid space. A ventricular tap released a sudden rush of air, which was followed by immediate clinical improvement. The patient remained in satisfactory condition for four days, when the pulse again fell to 56 per minute. Another ventricular tap again released a rush of air, and the patient immediately improved. Since the air was not absorbed, a third ventriculostomy was scheduled for the next day. During the night, the patient became comatose, the blood pressure increased and the pulse and respiration became slower. Death occurred within a few hours.

NEUROLOGIC DISCUSSION

DR. ROSS: In analyzing this case clinically there is evidence of congenital defects of the brain, manifested by mental deficiency, and of the skull in that her eyes were spaced widely apart, giving the impression of ocular hypertelorism. This latter is substantiated by the roentgenograms of the skull, which show the distance between the medial walls of the orbits to be 32 mm., whereas the normal distance is 26. The patient apparently progressed fairly well physically until the age of 16 years when she developed stumbling gait and falling, which would suggest a dysfunction of midline cerebellar structures. The beginning of severe headaches at the same time suggests an associated increase in intracranial pressure. Unfortunately, our information concerning the development of right hemiparesis at 18 is meager. If the onset was sudden and associated with an exacerbation of her symptoms, one would think of a cerebrovascular accident which, in the presence of the other congenital defects, would suggest vascular anomaly. If, on the other hand, the hemiparesis came on gradually and was not long sustained, it could be due to compression of the left cerebral peduncle or the brain stem associated with increased intracranial pressure. The only evidence of pyramidal tract damage on physical examination was the slight hyperreflexia on the right. This would support the presumption that the hemiparesis was due to pressure on this tract. The occurrence of what sounds very much like "cerebellar fits" in the presence of increased intracranial pressure points to a brain stem lesion. The coffee-ground vomitus could be due to blood swallowed at the time of the seizure or conceivably to a lesion of the hypothalamus with an associated gastric ulceration and bleeding. The irregular oligomenorrhea, obesity, and fasting blood sugar of 145 mg. are supportive indications of hypothalamic damage. The later development of more severe ataxia, headache and dysmetria of the left hand, falling to the left and nystagmus point to a subtentorial lesion affecting the cerebellum and its connections. Films of the skull were of little localizing value. For the most part they show evidence of long-standing increased intracranial pressure and the existence of ocular hypertelorism. Therefore, from a clinical standpoint our main evidence points to a lesion in the posterior fossa causing an obstructive hydrocephalus. Cerebellar tumor and ependymoma of the fourth ventricle are distinct possibilities, but the duration of symptomatology is against these. Furthermore, ventriculography showed no evidence of blocking of the aqueduct or of the fourth ventricle but rather indicated

an obstruction below this level. Adhesive arachnoiditis is another consideration but we have no history suggestive of an inflammatory or traumatic etiology. Although roentgenograms failed to show platybasia, assimilation of the atlas or axis to the occiput or other related anomalies in this region, the existence of a block below the fourth ventricle and the evidence of other congenital defects, namely, mental deficiency and hypertelorism, would lead me to suspect that we are dealing with an Arnold-Chiari deformity which has produced a severe obstructive hydrocephalus.

NEUROSURGICAL DISCUSSION

DR. HEIMBURGER: Even though there is a gradual progression of symptoms from infancy to death at 22 years, there are four outstanding periods in this patient's history. The enlarged head is evidence that she was not normal in infancy and that her difficulties started at that time. There are only a few causes for enlargement of the head in infancy. While subdural hematomas or macrocephaly may be the cause of increased head size, the most common cause is hydrocephalus, as was the case in this patient. As the enlargement of the head was proportionately less than the enlargement of the ventricles, some balance between the formation and absorption of cerebrospinal fluid was reached, probably before one year of age. This state of balance must have persisted for several years, as shown by the ability to balance the head and to walk. She also appeared to be quite bright during her first few years, which is a common finding in children with arrested hydrocephalus. The severe nature of her brain damage was demonstrated when she started to school and was unable to keep up with other children in classes.

The hydrocephalus remained compensated for many years, as she apparently grew and developed except in progress at school until she was 16 years old. At this time, frontal headaches and ataxia initiated the second period of her symptoms. There were no real remissions after the age of 16, but headaches continued for the rest of her life. Had the progression of symptoms developed without a history of previous difficulties, a neoplasm of the posterior fossa would have been suspected. This diagnosis was not supported by the long survival after the onset of symptoms, or by ventriculographic findings.

The minor convulsions appearing at the age of 19 started the third period in development of the patient's symptoms. The description of the convulsions helps in localizing the site of irritation. The momentary loss of consciousness can be localized to the diencephalon, while the hyperextension of the neck indicates irritation of the inferior surface of the brain and brain stem.

The fourth and last period in the sequence of symptoms began two months prior to the patient's admission with a major convulsion. This convulsion differed from the previous ones only in being more violent. Along with the increase in severity of the convulsions, her headaches became more troublesome and she was more drowsy, indicating that the increase in intracranial pressure was no longer adequately compensated.

Because of the duration of symptoms it is unlikely that the cause of obstruction was a neoplasm. One must, therefore, consider other causes for cerebrospinal fluid block. One is

meningitis with adhesions at the base of the brain, for which there is no evidence in the history. Atresia of the aqueduct of Sylvius could result in the sequence of events described, with periods of obstruction to the flow of cerebrospinal fluid followed by long symptom-free periods. The convulsions might have resulted from compression of the brain stem as a result of progressively increasing intracranial pressure. If one assumes that the air-filled space below the tentorium is a portion of the third ventricle displaced downward, one may postulate an atresia of the Sylvian aqueduct. The third possibility is an Arnold-Chiari malformation. This corresponds well with the exacerbations which occurred during periods of rapid growth and the remissions when growth was slower, allowing the cerebrospinal fluid dynamics to compensate. The symptoms and neurologic changes are similar to those described by Gardner and Goodall[1] in 17 adults with Arnold-Chiari malformation. He found that they had ataxia which affected the legs more than the arms, and usually one arm more than the other. This patient did not have platybasia, another condition which Gardner found to be common but not always present in adults with Arnold-Chiari malformation. One interpretation of the ventriculogram is that a small amount of air entered the cisterna magna. This is evidence against an Arnold-Chiari malformation, since the cerebellum and brain stem fill the cisterna magna in this condition. Another interpretation of the ventriculogram is that the air-filled space below the tentorium may have been the fourth ventricle displaced upward.

The use of a large volume of air for ventriculography was hazardous in this patient. It was thought, however, to be a worthwhile risk because of the recent observation that a ventriculogram by the "bubble technique" failed to demonstrate a large choroid plexus papilloma in a similar patient. In the case being presented, the failure of air to be absorbed caused a further increase in intracranial pressure. The dramatic relief of symptoms resulting from the removal of air and fluid with ventricular taps gave a false feeling of safety, and made a postponement of definitive surgery seem justifiable.

One of the reasons for presenting this patient is to emphasize the necessity for rapid action after air has been introduced in the ventricles, particularly in patients with hydrocephalus and closed fontanelles. Although hydrocephalic patients tolerate increased intracranial pressure for long periods, any procedure affecting the dynamics of the cerebrospinal fluid may cause rapid decompensation.

A third ventriculostomy was planned in this patient because it seemed to be the best way to allow escape of the cerebrospinal fluid from the ventricular system. It was considered that a posterior fossa exploration would eventually be necessary, but in view of the uncompensated increase in intracranial pressure, it was thought wise to postpone this procedure until normal cerebrospinal fluid dynamics had been firmly established.

The choice of diagnosis lies between atresia of the aqueduct of Sylvius and Arnold-Chiari malformation. Which of these two is correct depends upon the interpretation of the ventriculograms.

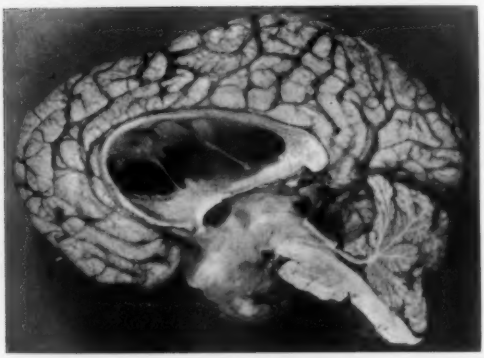

FIG. 2. Median section of the brain showing enormous dilatation of the third ventricle and normal size of the fourth ventricle. There is marked fenestration of the septum pellucidum.

CLINICAL DIAGNOSIS: *Hydrocephalus due to (1) Arnold-Chiari malformation? (2) Atresia of the aqueduct of Sylvius?*

ANATOMICAL DIAGNOSIS: *Hydrocephalus due to gliosis of the aqueduct of Sylvius.*

PATHOLOGY

DR. BAILEY: Upon opening the calvarium, the skull was found to be thinner than normal and many prominent depressions were seen in the inner table, corresponding in pattern with that of the cerebral convolutions. When the base of the skull was exposed, the sella turcica was found to be wider than usual and considerably flattened, with erosion of the anterior and posterior clinoid processes. Numerous pits were present in the floors of the anterior, middle and posterior cranial fossae. These three findings are indicative of very long-standing increased intracranial pressure. Pitting of the floor of the skull is produced by herniation of brain tissue into the arachnoid villi as the result of the elevated intracranial pressure, the herniations after some time leading to atrophy of the adjacent bone.[2] Further evidence of increased intracranial pressure was found in the tenseness of the dura together with flattening of the cerebral convolutions and narrowing of the sulci.

As seen in situ, the cerebral hemispheres were symmetrical and soft but uniform in consistency. On removal of the brain, the dilated third ventricle protruded above the lamina terminalis; this portion measured 1.5 by 1.5 cm. The brain was hemisected longitudinally after fixation in formalin (figure 2). Both lateral ventricles were widely and symmetrically dilated. The corpus callosum was thinned, and there were numerous large perforations of the septum pellucidum. With this exposure, it could be seen that the enormously dilated third ventricle had herniated through the incisura of the tentorium, the ventricle measuring 4 by 4 cm. The autopsy findings thus confirmed the second interpretation of the ventriculogram, namely that both air-filled cavities were portions of the third ventricle. The fourth ventricle was normal in size. There was no evidence of an Arnold-Chiari malformation. At the caudal end of the aqueduct, there was a septum which extended across and completely occluded the aqueduct.

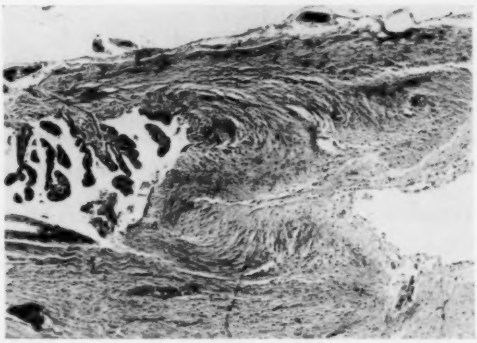

FIG. 3. Photomicrograph of the principal mass of glia occluding the aqueduct of Sylvius. Hematoxylin and eosin stain.

Complete autopsy on the organs of the thorax and abdomen showed no additional relevant findings. In particular, there were no congenital anomalies.

The microscopic changes in the cerebral cortex and basal ganglia were those of long-standing hydrocephalus. The septum in the aqueduct was composed of a solid mass of glia (figure 3). These appeared to be wholly astrocytic in routine sections, and there was insufficient material for differential stains. One margin was covered by ependymal cells and a tuft of choroid plexus lay nearby. About the septum there was considerable gliosis and for a few millimeters caudal to the main septum there were groups of astrocytes projecting into the aqueduct, some of them large enough to constitute complete secondary septa. Along the nearby ependyma there were multiple polypoid masses of neuroglia interrupting the continuity of the ependymal cells.

In Russell's comprehensive review of the pathology of hydrocephalus,[3] two conditions are listed which should be considered in classifying the present case. One of these is occlusion of the aqueduct by a neuroglial septum on a congenital basis. A neuroglial mass extending across the aqueduct is present in our patient, but figure 3 shows the adjacent ependyma smooth and wholly free of glial reaction. The more extensive gliosis in the patient being presented as well as the multiple secondary septa, with polypoid granulation along the ependymal surface of the aqueduct place our patient's lesion in the group designated gliosis of the aqueduct. The histologic changes are not those expected in a purely developmental anomaly, but they must have been initiated very early in life, as judged by the history. At the stage at which the material became available, there was nothing left but a scar, from which all traces of its production had disappeared. In considering the problem of etiology in regard to gliosis of the aqueduct, Russell discards the suggestions that it may be due to a malformation, to a tumor and to bacteria. She concludes, "The ependyma is apparently highly vulnerable and seems to have little, if any, power of regeneration. The subependymal glia, on the other hand, is capable of considerable proliferation when suitably stimulated. Hence it tends, in denuded areas, to protrude into the ventric-

ular cavity in the form of granulations. Individual granulations may . . . become confluent to form a complete investment over the remnants of disrupted ependyma. There are however no means as yet of proving whether such a process plays any essential part in gliosis of the aqueduct."

Whatever the etiologic agent is eventually proven to be, these facts must be taken into consideration in establishing its significance.

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Convulsions are frequent and important symptoms of cerebral disease. They occur under two conditions, apparently as the result of two different mechanisms. First, they occur if there is active irritation of the brain-tissue, such as is produced by inflammation of the brain or membranes, a growing tumor, or a sudden lesion. Secondly, they occur in what are termed "stationary lesions," in which the stage of activity is over, and such structural recovery as may be possible is taking place, or has taken place. In this case they are, apparently, due to the imperfect recovery of damaged nerve-cells, which regain the power of evolving nerve-force, but not the higher power of regulating its discharge. By each mechanism, convulsions are produced most readily when the disease is in the cortex. Stationary lesions scarcely ever cause convulsions unless they are situated in or near the motor cortex. Active irritation is most effective when in the same region, but it may cause convulsions whatever be its seat. They are also produced by general increase of intracranial pressure, and by diffuse processes, such as meningitis.

—Sir William Gowers, in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published 1885.

Neurology

BOOK REVIEWS

Brain Tumors of Childhood

Henry M. Cuneo, M.D. and Carl W. Rand, M.D. American Lectures in Surgery. 1952. Springfield, Illinois: Charles C Thomas, Publisher, 224 pages, $5.75.

This beautifully designed volume, dedicated to Max Minor Peet and Cobb Pilcher, is a review of 83 cases of brain tumor of childhood seen by the authors, presumably in the decade 1941-51. Each of the first 12 chapters deals with one pathological type of tumor. The thirteenth chapter discusses the symptomatology and differential diagnosis of neoplastic disease in childhood.

The experiences of the authors with cerebellar astrocytoma and medulloblastomas would probably coincide with that of most neurologic surgeons. The symptomatology of these two tumors is quite similar and even the longer course of the cerebellar astrocytoma is not a consistent differentiating point. The authors stress that the pathological diagnosis should be established by biopsy, since a therapeutic test of roentgen ray therapy for medulloblastomas may be misleading to the clinician and hazardous to the patient. The cystic astrocytomas of the cerebellum are more amenable to surgical procedures than the solid variety. The prognosis of the medulloblastomas remains gloomy in spite of the temporary relief given by x-ray therapy.

The other cerebral gliomas—glioblastoma, ependymoma and rare types—the authors state, fortunately encountered infrequently in childhood, do not have typical clinical pictures. Perhaps the exception to this dictum is the glioma of the pons, which by reason of the progressive involvement of cranial nerves and long tracts presents almost a pathognomonic syndrome.

Tumors about the third ventricle, craniopharyngiomas, pinealomas, and gliomas of the optic chiasm and thalami, usually present the symptomatology of generalized intracranial pressure although, as emphasized, the physical, neurologic or roentgenologic findings may suggest the precise location of the tumor. In most cases the authors consider ventriculography necessary; in fact, because of difficulty in diagnosing third ventricle tumors they "have come to feel that ventriculography should be carried out as a diagnostic procedure in every child suspected of harboring a cerebellar tumor" (p. 16) — a view-

point with which many neurosurgeons would not agree.

Papilloma of the choroid plexus is, in most reported series of brain tumors, a rarity, but Cuneo and Rand have three examples in their series. Their suggestion that these vascular neoplasms may be diagnosed by angiography raises the question of the possibility of making a pathologic diagnosis of brain tumors by this technique — a question which has not been answered adequately yet.

Meningiomas, when present in children, usually are large or have sarcomatous tendencies, so that their prognosis, unlike that of these tumors occurring in adult life, is poor. Thus the two patients suffering from meningiomas in the authors' series succumbed to their neoplastic disease.

The final chapters of the book deal with metastatic tumor and eosinophilic and infectious granulomata, lesions not usually included in brain tumor series.

A few well chosen case reports are used as examples of the different types of tumor and are illustrated by appropriate figures. The reader's interest is enhanced by timely quotations from authorities on brain tumors in children at the beginning of each chapter. A short and select list of references, almost all in English, is given for each subject.

Upon reading this treatise one has the feeling that little progress has been made in the handling of brain tumors in children since the monograph of Bailey, Buchanan and Bucy was published in 1939. This impression is probably due to the fact that the advances of the past decade are little emphasized by Drs. Cuneo and Rand. Although electroencephalography and angiography are discussed, with one exception, no illustrations are given, nor is their value in the diagnosis of neoplasms in childhood assesed critically. No reference is made to the use of radioactive isotopes for localization of brain tumor. Although the authors deliberately minimize the discussion of surgical procedures, the reviewer believes that some comment on the effect of the increased use of blood and blood substitutes and of the antibiotics on the operative mortality of brain tumors in children would be desirable.

In spite of these minor defections, this lecture is a scholarly, concise presentation of the subject of brain tumors of childhood, and should be read by all pediatricians, neurologists and neurosurgeons.

A. E. W.

Modern Headache Therapy

Arnold P. Friedman, M.D. 1951. St. Louis: C. V. Mosby Co., 127 pages, $4.00.

This small volume offers a very concise, well-organized review of the important field of headaches. The author has had a very extensive experience with headache patients in a number of clinics devoted exclusively to this complaint. He has summarized his wide experiences in this small volume. The book actually contains no new material. It is merely a review of many facts that have been well known to physicians for many years. This volume is primarily aimed at the practicing physician to whom it offers a brief survey of the knowledge that we have on this subject at the present time.

A. B. B.

Neurology

Management of Patients With Brain Damage

Joe R. Brown, M.D.

In the management of patients suffering from the effects of a damaged brain, one must keep many factors in mind. The direct physical effects of neurologic damage, the psychologic effects of brain damage, the general medical condition of the patient, the psychologic adaptation to disability, and the social implications of a handicapping illness are all to be considered. Of particular interest and importance in the diagnosis and treatment of patients with neurologic diseases are the limiting effects on adaptation imposed by the brain injury. These psychologic effects of organic brain damage form the focal point of this discussion. The theoretical aspects of the problem are gleaned from the literature on the subject. The semantics employed must be considered as largely the author's responsibility. Case material is presented for illustrative purposes and cannot be considered as documentary proof in any strict scientific sense. The practical application of the principles is based on clinical observations and interpretations.

Jackson[1] observed that the direct effect of an injury to the nervous system is the loss of function (negative symptom), while positive symptoms result from the "activity of nervous elements untouched by any pathologic process; that they arise during activity on the lower level of evolution remaining." He further pointed out that the highest functions of the nervous system are those which are most flexible, most complex, and most voluntary. In the presence of brain damage there is partial loss of these highest functions and the

From the department of neurology and psychiatry, Mayo Clinic, Rochester, Minnesota.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1951.

patient must resort to adaptive mechanisms which are less flexible (more organized), less complex, and less voluntary. In effect, the patient takes a step backward in the evolutionary or developmental scale, a process which Jackson called "dissolution"—a "taking to pieces." "In dissolution, the nervous system left is shallower, the top is then lower than normal, there is less of the person, less of the higher nervous arrangements." Goldstein[2] named this same process "dedifferentiation".

In discussing the highest mental functions, Jackson indicated that there are four major faculties: reasoning, ideation (including memory), emotion and volition. It is interesting to note how these presaged the four factors recently elucidated by Halstead.[3] Jackson's comments on the psychology of joking are used to delineate further these "highest nervous arrangements." In discussing puns he states: "We have the sensation of complete resemblance with the sense of vast difference. Here is, I submit, a caricature of the normal process of all mentation. . . . Recapitulating, I say that the process of all thought is double . . . is tracing relations of resemblance and difference, from simplest perception to the most complex reasoning." This is a description of the process we now know under the label, "ability to abstract." A patient suffering from the psychologic effects of brain damage resembles Jackson's description of the man with no sense of humor, "who takes things to be literally as distinct as they superficially appear, does not see fundamental similarities in the midst of great superficial differences, overlooks the transitions between great contrasts." He recognized that speech is a part of thought and that words "are necessarily required in all abstract thought." He recognized the higher value of the voluntary use of words as compared with inferior automatic, emotional expression of speech, considering the phenomenon as a further example of "dissolution". He had a broad concept of the interrelated functions of the nervous system and stated: "No one ever touched anything without moving his fingers. No one ever saw anything without moving his eyes." It is apparent that no one ever made a movement without feeling the results of the motion. Finally, each thought is accompanied by sensory experience and motor expression.

Since World War I Goldstein[2] has written extensively on the care of patients suffering from brain damage. He emphasizes the process of dedifferentiation, a concept which closely resembles Jackson's concept of dissolution. He further emphasizes that patients with brain damage have a loss of ability to abstract, and resort to concrete patterns of thinking and behavior. It would appear that he considers this loss to be an absolute one.

HALSTEAD'S THEORY OF BIOLOGIC INTELLIGENCE

Halstead[3] has recently contributed a usable, flexible, four-factor theory of biologic intelligence based on special psychologic testing and submitting the results to a factor analysis. From his studies of patients with brain damage, he infers that "biological intelligence is a basic function of the brain and is essential for many forms of adaptive behavior of the human organism." Bio-

logic intelligence is distributed throughout the cortex "in a gradient with its maximal representation in the cortex of the frontal lobes." He states that biologic intelligence is the biologic basis for the "ego" and has as its function the adaptation of the individual to external situations. Halstead[3] considers that biologic or adaptive intelligence consists of four factors: (1) a central integrative field factor C, (2) a factor of abstraction A, (3) a power factor P and (4) a directional factor D. Descriptively, the central integrative field factor consists of the organized background of the life experience of the person which permits the new to be interpreted and integrated. The factor of abstraction concerns the ability to recognize essential similarities and differences, to elaborate categories, and so forth. The power factor regulates affective forces and the directional factor determines the mode of expression. These four factors comprising biologic intelligence, or the ego, are selectively impaired by brain damage, leading to recognizable clinical symptoms. Conversely, the clinical symptomatology observed in patients with brain damage is best understood in terms of these four factors. Although psychologic testing[4] is much more specific in educing information concerning these factors, general neurologic testing and history taking will furnish considerable information. The cases reported in the remainder of this paper were selected because of the general absence of other signs and because psychologic evidence of brain damage was of outstanding importance in the management, diagnosis and treatment of the patient. The case reports will be presented as anecdotal evidence and were selected for their illustrative value.

ABILITY TO ABSTRACT

The ability to abstract is one of the basic factors of adaptive intelligence which is reduced in patients suffering from brain damage. This capacity includes the recognition of essential similarities in the presence of apparent differences, and in the reverse the recognition of important dissimilarities among things of marked superficial resemblance. The ability to grasp the essence of a given situation, to find a common denominator, to relate experiences in the proper categories, and to carry two or more criteria in mind at the same time are all a part of the ability to abstract. In its highest form it includes the use of symbols to represent the concrete object effectively.

One effect of brain damage is to reduce the ability to abstract. The patient is less able to trace fine resemblances and differences and has difficulty in simultaneously keeping in mind two or more aspects of the situation. Similarly he is slow to grasp the essential features of a new experience. Recurring similarities may be missed because of apparent and superficial differences leading to greater inaccuracies in the recognition of correct categories. Time and space relationships are less well appreciated. The effective use of symbols is limited leaving the patient more dependent on the direct evidence from his senses.

To evaluate a patient's ability to abstract it is important first to establish his previous level of intelligence. This may be accomplished by inquiring into

his schooling record, work record and general level of accomplishment. It may be verified by use of simple verbal scales such as that found in the Shipley-Hartford test. With such information as a standard one can test for digit retention, having the patient repeat digits forward and backward.

Another simple test is the use of verbal similarities. The patient is asked to tell how two things are similar – for example, apple and pear, bread and cake, house and barn, car and airplane, fly and tree. It is apparent that some of these pairs are more difficult than others. The normal person will usually say that an apple and a pear are both fruit. A patient with mild brain damage or with low intellect may say, "Well, they are both round on the bottom," or "They both have peelings." This suggests the responses are on a concrete, nonsymbolic level. With more severe brain damage the patient may be unable to see any similarity unless help is given and then may answer, "Well, you can eat them."

It is important at this point to test the patient's ability to keep two things in mind and to shift from one to the other. This may be accomplished by requesting the patient to give similarities and then differences. Patients with brain damage, once they make one approach to a problem, have difficulty in shifting to a second approach. They may repeatedly say that verbal similarities are not similar.

The nonverbal testing of the ability to abstract requires a certain amount of testing material and experience. However, a clinician not trained in administering psychometric tests can gain considerable information from the use of such tests as Koh's block design[5] or the Arthur stencils.[5] In difficult cases, the skills of a clinical psychologist will be required.

The following case illustrates how testing for ability to abstract led to the proper diagnosis and treatment.

A 44 year old male juke-box mechanic reported for examination on April 20, 1950 because of trouble with balance. He had been examined previously in 1940 with a chief complaint of rectal mass which was found to be an abscess. At that time he gave a history of dull headaches "all of his life," a period of sciatica on the right side in 1928, aching in the left arm, and two accidents involving blows to the head and unconsciousness during the 1930's. Neurologic examination in 1940 disclosed a rather bashful, tense individual with somewhat prominent eyes and rather marked symmetrical hyperreflexia of the deep tendon reflexes. Roentgenograms of the head were normal.

In April 1950 he complained of being clumsy and unsteady while putting on his trousers, his legs and arms seemed weak, he felt there was trouble thinking and making up his mind, and his left arm ached. His headaches were somewhat less troublesome. He was known to be a very self-effacing, apologetic, tense and depressed, but persistent individual who felt something was wrong with him. He found it difficult to verbalize his difficulties. The results of neurologic examination were not remarkable except for the exaggerated tendon reflexes noted ten years previously and hypoactive abdominal reflexes which had previously been normal. Roentgenograms of the head, the ocular fundi and the results of spinal fluid examination were all normal. The spinal fluid was under 9 cm. of pressure, the Kolmer reaction was negative, the value for total protein was 40 mg. per 100 cc., there was 1 lymphocyte per cubic millimeter, and the colloidal gold curve was flat. The neurologist who examined that patient was uncertain about the diagnosis and

advised a recheck in three months.

The patient returned on August 1, 1950, having spent the interval resting. He felt better generally but had some precordial distress and complained of difficulty making his left arm work properly. He felt less tense but noted increased fatigue and general weakness. There were no new findings on neurologic examination. The clinical psychologist was asked to carry out tests for organic brain damage, to be followed by personality tests if indicated. The Shipley-Hartford conceptual quotient was 59. The patient failed on the tests using the Partington pathways and the Koh's block design. The Bender-Gestalt and the Rorschach tests gave unmistakable evidences of brain damage. The Minnesota multiphasic personality inventory showed a personality with obsessive compulsive and depressive features. An electroencephalogram showed a grade 1 (on the basis of a maximum of 3) delta focus in the right Rolandic area. Because of the overwhelming evidence of brain damage and the rather minimal electroencephalographic finding, it was decided to carry out pneumoencephalography, which showed a large frontoparietal parasagittal tumor. At operation, a meningioma measuring 5 by 4 by 2.5 cm. was removed. Repetition of the psychometric tests one month after operation showed considerable improvement but the patient's condition had not yet returned to normal. At that time the patient was able to describe more clearly his previous difficulties in mentation. In particular he noted inability to understand written directions on how to assemble or repair new juke boxes although he was still able to repair ones which were familiar to him. It would appear that his ability to abstract was more involved than his background integrative abilities.

BACKGROUND INTEGRATIVE ACTIVITIES

The background integrative activities represent the organized accumulated life experiences of the individual. When faced with a new experience, one first begins to use the abilities to abstract described above. However, performing abstractly has little meaning or value unless it can be interpreted and evaluated in the light of past experience. Thus with each new experience there is a continually repeated comparison of the newly learned with the organized accumulated experience of the individual. The new is interpreted, a value is placed, a judgment is formed, and the whole is integrated into the background of life experiences.

Patients with brain damage demonstrate varying severity of restriction of the background integrative activites. With severe impairment, loss of memory and confusion are apparent. With milder involvement there is a restriction of the scope of integrative activities. One patient after a head injury was able to carry on in familiar surroundings but became lost outside his hotel when in a less familiar town. The reduced ability to abstract makes available to the patient information which is inherently faulty. This faulty information combined with restriction of integrative activities inevitably leads to faulty judgment and erroneous decisions.

One is able to sample the effectiveness of the integrative activities by specific psychologic tests. It is also possible to gain a working estimate by taking a careful history. Simple clinical sampling of integrative activities may be obtained by using simple calculations and inquiry into general information. The patient may be asked to give the meaning of a proverb such as "People who live in glass houses shouldn't throw stones." A typical "organic" answer is "glass breaks." The patient may then be given a simple printed

paragraph to read and give the meaning. Many times the history of impaired judgment will be obtained from a relative or employer as the chief clinical evidence of brain damage.

A 52 year old farm housewife was seen on August 16, 1950, with a chief complaint of fainting spells. These spells were not clearly described and appeared to vary in type. In one she lost her memory for several hours, in another she became blind for two weeks, in some she was unable to talk or see but was able to hear. In a few attacks she fell to the floor. Additional symptoms included a dead feeling of her right side, poor memory, dizziness, diminished hearing, tinnitus, diplopia, blurring vision, difficulty of reading, abdominal distress, intolerance to certain foods, generalized weakness, a lump in her throat, insomnia and crying spells. She had noted headaches all of her life. It was not possible to get a clear description of any of her symptoms. She stated, for example, that she was well until two years previously except that she had had an operation 12 years previously and had not been well since.

On general physical examination the blood pressure was 164 systolic and 100 diastolic, expressed in millimeters of mercury, there was a nodular thyroid, the liver was palpable, and the uterus had been removed surgically. Laboratory examination including investigation of the gallbladder and gastrointestinal tract gave entirely normal results. The patient was sent for neurologic evaluation. Except for a general hyperreflexia, results of the objective portion of the neurologic examination were negative. Roentgenograms of the head, the ocular fundi and visual fields were normal. The patient wrote poorly. On testing similarities she responded at a concrete level stating that banana and pear are alike because you eat them. She was unable to tell any similarity between a barn and a house. She failed completely on calculations stating that "4 plus 5 equals 20." She was unable to tell any meaning for, "Those who live in glass houses shouldn't throw stones." Although this patient did rather poorly on abstract thinking, her performance collapsed completely when faced with tasks requiring integrating activities. She finally stated that she even had trouble figuring out how to hang up the sheets by the corners at home. Pneumoencephalography revealed a dilated ventricular system and widened cortical subarachnoid spaces. The changes were more marked on the left side. It was concluded that this patient had a cerebral degeneration, either Pick's or Alzheimer's disease. This information was of considerable value in planning the future management of a patient whose complaints and bizarre history raised the question of differential diagnosis between hysteria and intracranial disease.

REGULATION OF AFFECTIVE FORCES

The regulation of affective forces is the third factor affected by brain damage. There are actually two major aspects involved although they may be likened to the two sides of a coin. A normal person has the ability to maintain his attention span and the energy to undertake reasonably prolonged conceptual thinking. At the same time he has the capacity to modulate the emotional responses of the moment for anticipated future benefit.

With organic damage to the brain, the affective forces may be impaired severely. Lacking adequate resources of energy (power) the patient with brain damage will be noted to have diminished spontaneity. His attention span is short and he is less able to maintain concentration on any given task. This leads to distractibility. There is a trend toward indifference and apathy with less concern about inaccuracies. Information concerning this can be obtained, usually from a relative, while the history is being taken. The sen-

sory examination will often give important clues for it may be necessary to keep calling for the patient's attention, and his responses will be inaccurate even though sensation is normal. He may call the examiner's attention to some irrelevant and nonessential occurrence which leads to the recognition of the patient's distractibility. Recently one such patient interrupted the sensory examination to say that it would be necessary to wait until he scratched his arm. Incidentally, at that point he also yawned. In addition to the lack of adequate "drive", the defective ability to abstract, to integrate and project to the future the essential significance of an experience also contributes to the indifference, apathy, carelessness and distractibility of patients with brain damage. The following case clearly illustrates these phenomena.

A 31 year old male truck driver was overcome by carbon monoxide on February 9, 1950, while driving a truck and was found unconscious and cyanotic at a roadside eating place. He was given emergency treatment in a local hospital. He remembered becoming sleepy and stopping the truck but did not remember getting out of the cab. Two weeks later when first seen at the Mayo Clinic he gave a normal response on objective neurologic examination. Calculations were fair but he made three mistakes on serial subtraction of 7 from 100. An electroencephalogram showed a mild, left temporal delta focus and some general dysrhythmia. He returned to work one month after the original incident. After one month at work his employer requested a recheck because the patient was less reliable.

He had incurred a traffic violation costing the employer $100, had run a truck off the road on one occasion, and on a third occasion had backed into the employer's car five times while trying to pull out of a parking place. The patient had always been a resourceful and reliable workman but he now lacked initiative at work. The electroencephalogram showed no abnormality and the Wechsler-Bellevue test failed to show evidence of deterioration. Clinically, however, he was noted to lack spontaneity and initiative. He was deliberate and passive, almost to the point of negativism.

In August 1948 the patient was brought for a revaluation. His behavior pattern had deteriorated to one of marked indifference and apathy. His daily activities included getting up at 9 a.m., eating breakfast and going to the beer parlor. He would go home for lunch, look at a magazine and return to the beer parlor. He would go home for supper and return to the beer parlor until bedtime. For the past month he did not drink while at the tavern. The electroencephalogram was normal. The Rorschach test showed lack of drive to attempt anything difficult, little responsiveness to outside stimuli, passiveness, and general personality constriction. The Shipley-Hartford conceptual quotient was 55 (the critical score usually being considered as 75). The Bender-Gestalt, Partington pathway, Koh's block, and Porteus maze tests all consistently showed evidence of brain damage. It has subsequently been impossible for this patient to make any vocational readjustment. Indifference, apathy and lack of initiative continue to be the outstanding clinical symptoms.

The other aspect of the regulation of affective forces lies in the modulation of emotional responses. The intact mature person is characteristically able to maintain reasonable regulatory control over the anxieties, tensions, irritations, angers, depressions, and euphoric feelings of the moment in the interest of social adaptation and future gains. With organic damage to the brain the emotional responses become increasingly governed by the stimulus of the moment. Consequently such patients become unadaptive, capricious and impulsive. They tend to be stubborn and quick to anger at slight provocation.

Depression at a mildly sad situation may alternate with euphoria in rapid succession.

In instances of milder brain damage the phenomena observed differ somewhat from the above. Such patients become tense and anxious when faced with a new situation or when placed under stress. At the same time because of the defects of abstraction and integration they are less able to adapt to the new experience. Because of difficulty in modulating emotional responses they are less able to tolerate the anxiety. Under such circumstances some patients will show overt signs of tension and even free floating anxiety. Other patients will rely on varying defenses against anxiety. Depression, fatigability, somatic complaints, and rigid compulsiveness are among the common defenses observed. Irritability, resentment and hostility may be observed. An occasional patient will accomplish this defense by a relatively complete withdrawal from all new experiences. This phenomenon has been described by Goldstein[2] as the "catastrophic reaction." In the following case the chief evidence of brain damage was observed as a difficulty modulating emotional responses.

A married woman aged 25 was first admitted to care at the Mayo Clinic on November 1, 1950, with an acute spontaneous subarachnoid hemorrhage which had begun at 9 p.m. the previous night. She had a left homonymous hemianopsia and subsequent history suggested that it dated back as far as 1942. The exact time and mode of onset of the hemianopsia could not be determined. Angiography disclosed a large arteriovenous angioma involving the angular branch of the right middle cerebral artery with a large arteriovenous shunt via the vein of Labbé. A craniotomy was performed in the hope that the main arterial supply might be occluded with clips and sectioned. This was not possible and several large vessels were stroked with a ball-tipped coagulating point of the electrocoagulator. One vessel was ligated. The wound was closed without incident. The convalescence was satisfactory, the patient having only occasional headache. She was allowed to dangle her legs on the fourteenth postoperative day and was dismissed from the hospital on the twenty-first postoperative day.

The patient returned for re-examination in January 1951, with complaints of headache, dizziness, weakness, nervousness and a black-out spell. She had the previously noted left homonymous hemianopsia. There was a moderate weakness of the left arm and leg which were considered to be hysterical in origin. Psychiatric consultation showed evidence of a complicated, long-standing and deep-seated neurosis. In addition she was very disturbed because since her subarachnoid hemorrhage and operation she had noted diminished capacity to repress tension. She felt loss of confidence in herself, had been irritable toward her husband and children, and had been uncomfortable if people saw her walk. The fundamental neurosis dated back to the earliest days of childhood and her relations with her father and mother. She had experienced feelings of depression and occasional obsessive-compulsive behavior alternately with bursts of irritability. She was just able to keep things in order until her subarachnoid hemorrhage and craniotomy. Since that time her repressive powers had been completely disorganized. These combined factors led to the development of the somatic complaints and conversion symptoms, noted on her re-evaluation. Prolonged psychotherapy was considered the only possible solution to this particular problem.

VOLUNTARY SELECTION OF ADAPTIVE BEHAVIOR

The voluntary selection of adaptive behavior is the fourth factor affected by brain damage. Under ordinary circumstances it is certainly true that much of our adaptive responses result from reflex, automatic mechanisms or from

largely unconscious motivations. Such responses must indeed save us a remarkable amount of effort and time. However, the very nature of reflex, automatic, organized and unconscious mechanisms decrees that such responses must be relatively rigid, stereotyped and inflexible. They may be ideally adaptive for fixed situations but they tend to be unadaptive to the new and changing. It is then that we must rely on our most highly flexible, most voluntary, most complex adaptive resources. The use of the ability to abstract, the integration of the new into the framework of organized experience, and the regulation of affective forces are literally a means to an end. That end is the exteriorization of adaptive intelligence as a response to the new experience, through motor performances, sensory modalities and physiologic concomitants.

The patient suffering from brain damage has diminished capacity voluntarily to select and direct adaptive behavior on a truly complex flexible level. He is forced to resort to mechanisms which are more automatic, more organized, and simpler. Instead of calculating mentally, he may be forced to substitute the simpler, more concrete method of counting on his fingers. He tends to approach new problems with a predetermined attitude and he interprets the new on the basis of that attitude. When he has solved a problem he is less concerned with the correctness of his solution than he was formerly. He will then persistently attempt to utilize the last "successful" solution even though it does not apply. This phenomenon is recognized as perseveration. His responses tend toward the rigid, stereotyped, and unadaptive because he cannot readily and voluntarily shift to a new attitude or response. Because new situations no longer have the same significance for him he may appear distractible or may pay undue attention to irrelevant stimuli and appear absent-minded.

There are no simple tests which a clinician can apply to sample specifically the patient's ability to direct and select adaptive responses. However, information may be gained from inquiring about the patient's behavior from relatives. In addition, during the course of taking the history from the patient one can get hints concerning rigidity and compulsive behavior. During the neurologic examination one gains definite information concerning tendency to perseveration, lack of ability to shift to a new approach, absent-mindedness, distractibility, and stereotypy. If psychologic testing material is used in the examination, one can also be alert for these phenomena while administering the tests. One patient gave as an important complaint the difficulty he noted in controlling his adaptive responses.

A 52 year old male office worker of superior intelligence reported for examination in July 1950. He had multiple complaints including prominence of the veins of the left hand, swelling of the left ankle, pressure sensation in his head, diminished hearing in the left ear, five attacks of momentary unconsciousness, shortness of breath, and numbness of the left thigh. In 1945 a meningioma had been removed from beneath the left temporal lobe by a prominent neurosurgeon. In 1949 a mass had been found in the left external auditory canal which proved to be a meningioma.

On examination, there were no significant general physical abnormalities. There was markedly diminished hearing in the left ear but no local evidence of recurrence of tumor in the external auditory canal. The left zygoma was enlarged. Roentgenograms of the head and mastoids disclosed evidence of sclerosis of the left temporal bone, mastoid process, and zygoma due to infiltration by tumor. There was evidence that a left parietotemporal craniotomy had been performed. The ocular fundi were normal but a right homonymous, upper quadrantanopsia was found on a test of the visual fields. Neurologic findings included a slightly hyperactive right biceps reflex and a zone of hypesthesia in the distribution of the left lateral femoral cutaneous nerve. On testing for aphasia it was noticed that he occasionally had a little impairment in selecting the correct word, he had slight difficulty in comprehending complex material, and he had a little trouble shifting to new items. He was compulsive, meticulous, and carried a folder of information about himself. One of his complaints was that he felt the need to be persistent about things, although he knew it might be foolish and a nuisance. He felt angry within himself and had difficulty in keeping from showing it. On one occasion he spent two hours straightening out a mix-up on a telephone call that had been placed. He was forced within himself to persist until he had it settled. This incident required that he talk in succession to the operator, the chief operator, the assistant manager and the manager, although only 15 cents and an incorrectly placed phone call were involved. Since his brain tumor had developed, he had repeatedly noticed this loss of control over his own actions.

In the foregoing portion of this paper attention has been focused on the major psychologic effect of damage to the brain. The description of the four known factors of importance may have left the impression that these factors are independent of each other and that one factor could be diminished without affecting the others. A study of the case reports, however, will show how interdependent these various factors are even though the deficit may appear externally to be predominantly of one factor. It is similarly true that the restriction of personality resources as the direct effect of brain damage does not occur as an isolated phenomenon. It occurs in the setting of a constellation of forces which are interacting within and on the patient. In managing such patients one must consider the total resources and deficits of the person—physical, intellectual, emotional, social and financial. It is helpful to study the defects first to gain an idea of the limits imposed on any treatment. This should be followed by a study of the resources which may be utilized in an effort to compensate for the deficits. It is generally necessary to be willing to accept a goal which is below the ideal.

Confusion, apathy and euphoria are most commonly seen in patients with relatively severe brain damage. Such patients seem to do best on a simple routine of living. One must generally limit the number of visitors and avoid situations which are complicated. It is important to have a schedule of daily activities including hygiene, simple entertainment, and a few simple tasks to prevent further regression.

With milder involvement the common clinical manifestations include depression, fatigability, somatic complaints, and occasionally conversion reactions. Anxiety, tension symptoms and reactions of increased rigidity tend to appear especially when the patient is placed under stress. Treatment in such instances must be individualized. One 69 year old widow with diabetes and

generalized arteriosclerosis was seen because of severe pains in the extremities presumably initiated by a mild diabetic neuritis. The patient's daughter was distraught by the continuing demands made by the mother and by loss of sleep. A program was outlined which would be within the capacity of the patient's restricted adaptability. This program included mild sedation, an ounce of whiskey three times a day, and analgesics as needed so that she no longer needed to wheedle for relief of pain. A routine of living included fixed hours of rising, dressing (including shoes, instead of slippers), eating, listening to the radio or watching television, and responsibility for a few simple tasks. One year later the patient returned for a re-examination. She had gained 30 pounds, was free of pain, and both the patient and daughter were happy.

Contrasted with this therapeutic approach was that used in a 30 year old mother of four children who had suffered a right hemiplegia and had the mild residual of an aphasia. She was depressed and rather compulsive. Through encouragement and support she was gradually able to take on more activities. She was advised to use the afternoons for activities which required initiative. Routines were de-emphasized and the patient was gently encouraged in the direction of greater spontaneity and flexibility.

A 34 year old garage mechanic had suffered a head injury six years previously. After one year he was able to work full time without significant symptoms. He was thoroughly familiar with ignition work and was able to do it well. Four years later, to earn more money, he became a general mechanic. The flexibility required for shifting to different jobs several times a day was difficult for him owing to his diminished ability to abstract and integrate. Headaches, tenseness and giddiness developed. He was advised to return to the more restricted and routine work which was within his capacity.

SUMMARY

The diagnosis and treatment of patients suffering from brain damage require an evaluation of many factors. The restriction of adaptability may become apparent as a diminished ability to abstract, to integrate, to regulate affective forces, and to direct behavior. These factors may be sampled by clinical observation and by specific testing. An adequate program of treatment must be individualized in accordance with the patient's deficits and resources.

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Neurologic Symptoms Following Accidental Intraspinal Detergent Injection

N. W. Winkelman, M.D.

CAUDA EQUINA and spinal cord symptoms following spinal anesthesia have been reported, some as the result of the anesthetic solution itself and others from secondary infections. In the 11 cases to be reported here, a detergent was accidentally injected intrathecally with the spinal anesthetic.

The clinical picture might be divided into four stages and in some patients all four stages could be observed. The first can be named the cauda equina stage. In this the signs and symptoms are the result of limitation of the pathologic process to the cauda equina.

The second stage can be termed that of spinal cord symptoms, in which damage to the spinal cord is added. This includes root symptoms, depending upon the level of involvement, as well as injury to the cord itself and its membranes. In many cases pyramidal tract and posterior column signs and symptoms become evident and frequently a definite sensory level can be determined. In some cases signs of a spinal fluid block appear.

The third stage in the symptom-complex could be termed cerebral, and manifestations usually follow the spinal cord evidences or appear *pari passu*. Included in this category are headache, apathy, confusion, cranial nerve signs, including single or bilateral seventh nerve paralyses, and abducens weakness or paralysis. The rest of the cranial nerves are usually unaffected.

The final or fourth stage of symptoms, which are usually terminal, continue the upward march of the pathologic process. Here increased intracranial pressure is the outstanding manifestation, with progressive internal hydrocephalus as the basic mechanism for the symptoms. All patients who developed this last stage of signs and symptoms died with evidence of marked intracranial hypertension. Two of these patients were operated on (ventriculostomy) in a vain effort to halt the inevitable progress of the condition.

The group of cases to be reported here differs from those previously cited in the literature in several ways. 1.) The sequelae usually came on within a few days after the intraspinal anesthesia and not, as reported, by Kennedy

From the department of neuropathology, University of Pennsylvania Graduate School of Medicine, Philadelphia.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1951.

et al,[1] weeks or months after the operative procedure. 2.) In about half the cases a cerebral complication occurred which could be attributed to a so-called cerebral "arachnoiditis." In one case uniform ventricular dilatation was found by ventriculogram performed through the ventriculostomy tube. The fluid was under very high pressure. 3.) Recovery in the milder cases began quickly, even after a complete flaccid paralysis of the legs had occurred. In six cases out of the 11 practically complete recovery ensued. 4.) In an effort to determine the etiologic factor in these cases suspicion was first directed against the anesthetic solution, and it was found that at least three different preparations were used. Investigation of the method of sterilization disclosed no slip-ups, except in cleaning of the syringes before autoclaving. Here the procedure was to wash syringes in a mild detergent solution and to rinse once or twice in tap water before autoclaving. Injection of a similar mild detergent solution into an animal produced paralysis of the hind legs. It was then reasonable to conclude that the spinal and cerebral symptoms were the result of varying amounts of detergent entering the subarachnoid space, and the greater the concentration, the more severe and extensive the damage and resultant symptom-complex.

REVIEW OF THE LITERATURE

Neurologic complications following spinal anesthesia have recently been reviewed by Kennedy, Effron and Perry.[1] They discussed the result of damage to the roots and spinal parenchyma by the anesthetic solution itself, but no comment was made about the effects of introduction of bacterial agents into the subarachnoid space. These are well known and do not differ in any great degree from infections from any other route. As far as is known there has been no counterpart to the cases described in this paper. No one has been able to determine that the damage to the roots, membranes and parenchyma of cord and brain has been due to the introduction of a chemical agent with the spinal anesthetic solution.

In 1945 Kennedy, Somberg and Goldberg[2] reported three verified cases of spinal arachnoiditis and paralysis following spinal anesthesia. They also stressed the gravity of injecting a spinal anesthetic solution into the spinal canal.

The closest parallel to the cases that are described here was a case report by Kamman and Baker[3] where a patient of 66 had had two spinal injections within a comparatively short period of time. His symptoms paralleled those described here. However, his condition lasted much longer. After a period of seven months, and coincident with some return of motion in the paralyzed muscles and some return of sensation, the patient's temperature began to rise and he became cyanotic, drowsy and vomited several times. Twenty-four hours later he had a convulsion. His temperature rose to over 105 degrees. There was deviation of the right eye outward and the right arm was spastic and was held in flexion. He gradually failed, the temperature rose to over 108 degrees, and death occurred 16 hours after the convulsion. A complete

FIG. 1. Ventriculogram, lateral view, showing uniform dilatation of entire ventricular system.

autopsy was performed but the brain and meninges, which were normal grossly, were not studied microscopically. The spinal cord showed evidence of an arachnoiditis with destruction from the level of the midthoracic to the upper lumbar regions.

CASE REPORTS

Case 1.—A boy aged 17 was operated on for acute appendicitis under spinal anesthesia early in 1950. Within 24 hours he developed incontinence and mild delirium and complained of numbness in both feet. He was discharged on the fifth day as surgically recovered, but three days later he noted weakness of legs which progressed in the course of a week to complete paralysis with complete loss of control of sphincters. An associated left internal strabismus with left peripheral facial weakness also developed. Childishness, mental obtunding and slurring speech followed. Then came severe headache, nausea, vomiting and pain in the back of the neck; slowing of pulse and right facial weakness soon followed. The temperature was not elevated.

Spinal puncture two weeks after onset showed cloudy fluid with initial pressure of 410 mm. of water, with 5 cells; chlorides, 732 mg.; and protein, 11 mg. Skull roentgenogram was negative.

In the next four days the intracranial pressure rose to 600 mm. of water and remained at that point with very little relief by ventricular drainage. In the course of the next week the patient had occasional generalized convulsions despite anticonvulsant therapy. A ventriculogram showed cortical atrophy, with symmetrical dilatation of the entire ventricular system. There was no evidence of displacement or encroachment on the ventricular system (figures 1 and 2). Death occurred two months after the spinal anesthesia.

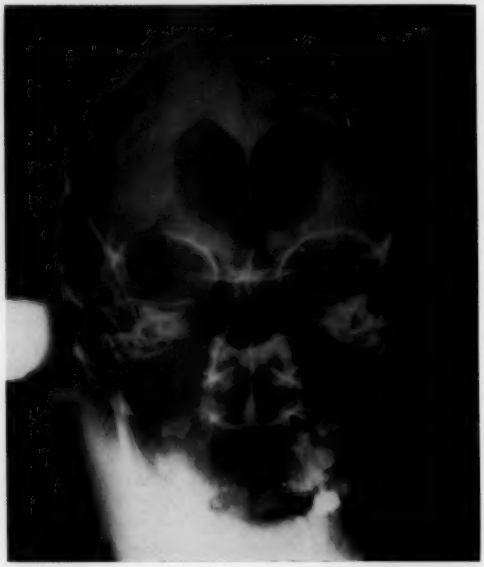

FIG. 2. Ventriculogram, posterior-anterior view, showing ventricular dilatations.

Case 2.—A girl of 16 was operated on for acute appendicitis under spinal anesthesia. Three days postoperatively she developed urinary retention which subsequently cleared. Two days later she suddenly found that she could not climb steps. It was noted at this time that there was bilateral 7th nerve paralysis. She was readmitted to the hospital three days later.

On admission temperature, pulse and respirations were normal. The blood pressure was 120/90. There were bilateral 7th nerve palsies and flaccid paralysis of both lower limbs. Initial spinal puncture: pressure 140 mm.; 14 cells; total protein, 120 mg.; sugar, 76 mg.; chlorides, 666 mg. On the day after admission there was apparent improvement but within three or four days the patient had pains around the chest and down both arms, with nuchal rigidity and generalized areflexia. Within a week the patient had a generalized convulsion. Spinal puncture at that time showed partial spinal block and the fluid was xanthochromic, with total protein of 350 mg. and with 49 cells. Despite this ominous evidence the facial weakness was clearing up. Later the patient had three convulsive seizures.

A day later examination showed a sensory level at the 6th thoracic dermatomere. The 7th nerve weakness was practically entirely cleared. A few days later further convulsions occurred. The patient became somnolent and the neck rigid.

Four days later there was an increased number of generalized convulsions with a temperature rise to 105 degrees. On that day a burr hole was made over the posterior horn and the fluid was found to be crystal clear but under high pressure. A catheter was inserted into the ventricle. In 24 hours the patient brightened, temperature decreased and ventricular pressure went down to 300 mm., but within a week, despite the drop in ventricular pressure and lowering of temperature, the patient became apneic, the pulse dropped and there was eventual complete respiratory arrest.

Case 3.—A man, aged 62, with a history of urinary obstruction, had a prostatectomy in two stages. The second operation was done under spinal anesthesia, and eleven days

later he developed weakness of legs, incontinence of sphincters and a decrease in perianal sensation. The exact sensory picture was impossible to delimit clearly in view of the fact that the patient's sensorium was clouded. He showed tremulousness of muscles and general motor weakness throughout the body, particularly in the lower limbs. The Achilles reflexes were absent from the outset, and patellar reflexes were just barely obtained.

Within a few days the patient's lower limbs became completely flaccid and there were trophic ulcers at the heels and sacrum. The mental cloudiness grew worse to the point where the patient was completely out of contact with his surroundings. Death occurred 34 days after the onset of the original symptom of weakness of the legs.

Examination of the spinal cord grossly showed no abnormalities but the membranes and cord were cut transversely for microscopic study. The microscopic sections in the myelin sheath stain showed a small cord. There was a marginal status spongiosus (figure 3). Both anterior and posterior roots showed degenerative changes, more marked in the lower cord. The pia was thickened, fibrotic and adherent to the under-surface of the dura and to the cord margins. The subarachnoid space was obliterated in places, especially in relation to the posterior aspect of the cord. Areas of demyelination were seen in the posterior and lateral columns of the cord, especially in the thoracic region (figure 4).

The cell stains confirmed the hyperplastic changes in the pia, the absence of inflammatory reaction and changes in the entire periphery of the cord in the nature of a status spongiosus. The ventral horn cells showed fat infiltration and retrograde degeneration. The anterior and posterior roots showed degenerative changes of varying degrees. The fibrillar stains (Klarfeld) (figure 5) showed new formation of connective tissue within the subarachnoid space, in places completely obliterating that space. There had been compression of many of the nerve roots in relation to the subarachnoid space. Nerve fiber stains (Bodian) (figure 6) confirmed the degenerative changes of the axones at the cord margins. It also showed poverty of the fibers within the nerve roots. Fat stains (scarlet red) showed an excess of lipoid within the ventral horn cells.

Case 4.—A woman of 44 was operated on early in 1950 for a cystic ovarian tumor. The patient did well until the fifth postoperative day, by which time she was at home. She found that she could not ascend the stairs and she could not control urination or bowel movements. Gradually she developed weakness in both lower limbs along with severe pains in the back. There was loss of feeling in her legs.

When seen at home four weeks after the onset of the condition the cranial nerves and ocular fundi were normal. The upper limbs were entirely within normal limits. In the lower limbs there was tenderness and flabbiness bilaterally with a slight increase of patellar reflex on the left and absence on the right and absence of Achilles reflexes bilaterally. There was decrease of sensation in the perianal area in the distribution of the 3rd, 4th and 5th sacral segments, especially on the right. Sensory examination of the legs showed hypalgesia of L2, L3, L4 on the left and of L5 and S1 on the right. Walking was difficult and assistance was necessary because of weakness of the entire right lower limb.

Five weeks later the patient was able to come to the office, but required the aid of a cane due to weakness of the left leg. At that time there were no symptoms or signs above the waist. The perianal hypalgesia was still present bilaterally and it had contracted down to S4 and S5 bilaterally. The patient now had regained control of the sphincters, but the legs were still flabby and tender. The patellar reflexes were now exaggerated bilaterally and the Achilles reflexes could just be obtained. There were no sensory changes in the lower limbs.

As time went on the patient's condition continued to improve until five months after operation when she was able to walk without the aid of a cane, but she was still weak in the lower limbs. It appears that this patient will make a fairly complete recovery.

Case 5.—A patient, aged 38, had a cesarean section under spinal anesthesia. On return to her room her legs and buttocks remained numb, while sensation on the abdomen re-

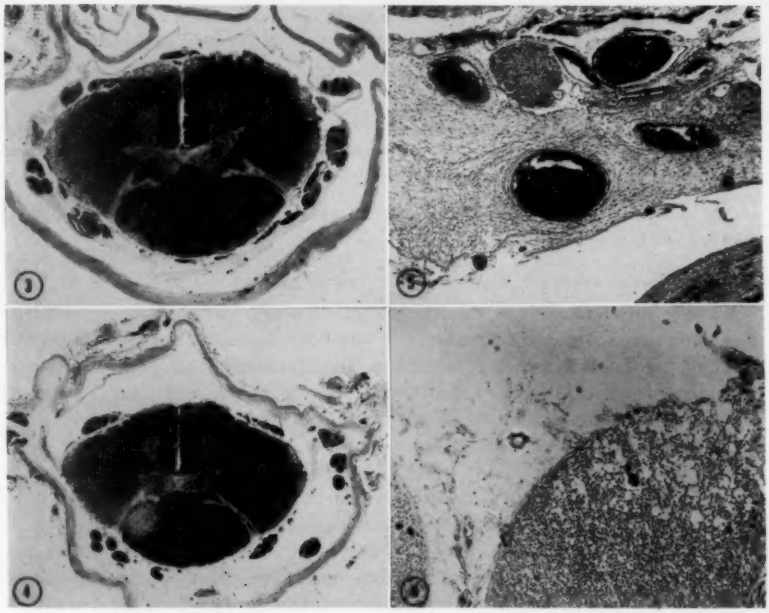

FIG. 3. Thoracic cord, showing marginal status spongiosus (Weil stain). FIG. 4. Thoracic cord, showing degenerative patch in posterior column and marginal status spongiosus (Weil stain). FIG. 5. Thoracic cord. Subarachnoid space showing fibrosis of pia with compression of roots and venous congestion (Klarfeld stain). FIG. 6. Status spongiosus. Ventral pyramidal tract with implication of ventral root. (Bodian stain X).

turned. Numbness in the legs persisted during her entire hospital stay, and upon discharge became intensified on the right. Her legs seemed to collapse under her. Ability to walk decreased and she was forced to climb stairs by pulling herself up on the bannister and hand rails. Within a few weeks she became completely bedridden.

She was readmitted to the hospital with complete paraplegia. There was perianal hypalgesia. Deep reflexes in the lower limbs were absent with an equivocal bilateral Babinski. There was distinct weakness of the rectal and vesical sphincters. The initial spinal fluid study showed a clear fluid under a pressure of 120 mm. of water. It contained 4 cells with a total protein of 60 mg.; sugar, 90 mg.; and chlorides, 602 mg. One week later the total protein was 120.

Physical therapy was given and the patient made slow but progressive improvement. Within a period of two months there was gradual return of power in the lower limbs. Sphincteric control was regained. The saddle hypalgesia gradually disappeared. When seen six months later the patient was practically entirely recovered, with only slight weakness in both lower limbs, especially on the right. She has since made a complete recovery.

Case 6.—A 45 year old man was operated for a hernia under spinal anesthesia. He complained of difficulty in voiding immediately afterwards and bowel function was also disturbed. Within a few days he experienced difficulty in walking and shuffled his feet.

On neurologic examination 16 days after the operation, the patellar reflexes were increased bilaterally but the Achilles reflexes were barely obtainable. A Babinski sign was present on the right, but there was no clonus. Marked weakness prevailed in both lower limbs, with hypalgesia perianally in S1, S2 and S3 distributed bilaterally. Spinal fluid examinations were not done.

The patient remained in the hospital over a month and during this time some improvement resulted. Within five months after discharge he had improved to the point where he was able to carry on his work as a merchant, and he had regained complete control of his sphincters.

The other five cases will not be detailed since they had all the features described in cases 4, 5 and 6, with eventual recovery.

CONCLUSIONS

In this presentation the inadvertent introduction of a detergent solution in conjunction with a spinal anesthetic has been found to have a deleterious effect on the cauda equina, spinal roots, cord parenchyma, cord membranes, cranial nerves and cerebral membranes. A progressive ascending symptomatology was initiated which could eventually be predicted in succeeding cases step by step from the cauda equina syndrome upward. In only a few cases did the involvement eventually reach the membranes of the brain. When this occurred an intracranial hypertension was produced which could not be controlled, even with radical measures including ventriculostomy.

It is interesting, although probably only a coincidence, that in the beginning the cases resembled a Guillain-Barré syndrome. It was also interesting that, as in the latter syndrome, the cellular content of the spinal fluid was low and the protein high. Similar cranial nerve defects occur in both conditions.

The pathologic process consisted of a demyelinization of the spinal roots beginning with the cauda equina, with a marginal demyelinization (status spongiosus) of the spinal cord itself. A hyperplastic pia was one of the outstanding features and could readily explain many of the symptoms, including root disturbances, level symptoms and eventually a secondary internal hydrocephalus.

The symptomatology depended on the concentration of detergent introduced into the spinal canal. In those cases where only a small amount of detergent was injected the symptoms were limited to the lower spinal roots and recovery eventually resulted in from six to twelve months. With greater concentrations of the detergent more and more of the central nervous system and membranes were involved. One of the interesting features was the very rapid production of ventricular dilatation, as shown by ventricular air study. Within a period of just a few weeks there was sufficient ventricular dilatation to justify designation as internal hydrocephalus. Headache and other evidences of increasing intracranial pressure were present. Surgical attempts to relieve this one feature failed in two cases.

It is rather interesting that occasionally improvement in the cauda equina picture occurred while progressive cerebral involvement was going on. The cranial nerves affected were the 7th, bilaterally, and the 6th, at times bilaterally.

SUMMARY AND CONCLUSIONS

1. Eleven cases are reported in which a detergent solution was accidentally introduced intrathecally along with a spinal anesthetic agent.

2. Depending on the concentration of the detergent, a group of symptoms was initiated beginning with involvement of the cauda equina, ascending the spinal cord and its membranes and eventually producing a fluid block over the vertex of the brain as the result of hyperplasia of the soft meninges with resulting symmetrical ventricular dilatation.

3. In those cases with internal hydrocephalus, death resulted despite surgical intervention.

4. In cases with cauda equina involvement alone improvement began comparatively early and continued until a return to normal or near normal was accomplished.

5. Pathologic examination of one of the cases that died showed a hyperplasia of the pia with compression of roots along the entire spinal cord. Marginal degeneration of the spinal cord was evident, giving the appearance of the so-called spinal "halo".

6. The suggestion is made that every step in spinal anesthesia must be carefully supervised by the anesthetist himself, since laxity in the preparation of syringes was held responsible for the resulting damage to the central nervous system. In four cases death resulted from a progressive internal hydrocephalus.

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The causes of inflammation within the spine are, principally, blows or falls, violent muscular efforts, and exposure to damp or cold. One patient became affected with acute spinal myelitis from being long exposed to the rain and cold in an open boat. This affection has frequently occurred from the pernicious custom of lying upon the damp grass. Rheumatism seems occasionally to have led to this disease. The observations of M. Louis (*Mémoires sur Diverses Maladies*) have distinctly shown the connection between caries of the vertebrae and spinal myelitis.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

Significance of Cerebral Fat Embolism

Alexander Silverstein, M.D.

CEREBRAL FAT EMBOLISM is a well established clinico-pathologic syndrome which has received very little study in the field of neurology. With the exception of Courville[1] textbooks in neurology and neuropathology either omit or merely touch upon the subject. In 1937 Courville wrote as follows: "If the invasion of fat in the circulation is overwhelming death may be immediate; if less severe the patient may continue in a stuporous or delirious state which may be so marked as to require confinement in a psychopathic institution." In spite of this provocative statement, as well as numerous contributions emphasizing its practical clinical importance in trauma and many other conditions including head injuries, fat embolism is not only ignored clinically but is frequently unrecognized at necropsy. This is due to the prevalent utilization of paraffin sections for routine study. The use of fat stains in frozen sections is essential for the proper recognition of the condition.

LITERATURE

The literature on fat embolism is voluminous. It begins with the experimental work by Lower[2] in 1669 and Magendie[3] in 1821. The important role of the brain in this condition is credited to early investigators as Von Bergman[4] in 1873, Scriba[5] in 1880 and Payr[6] in 1899, who distinguished the cerebral from the pulmonary form of fat embolism. Interesting to neurologists are the reports by Dejerine[7] of two fatal cases, one following fracture of the right parietal bone, and Frazier[8] who referred to three cases of fat embolism following forcible straightening of stiff joints.

The most comprehensive contribution in American literature was made by Warthin[9] in 1913, who wrote, "The medico-legal significance of fatty embolism is wholly disregarded at the present time in this country. As it is the cause of death from apparently slight as well as more serious injuries to bones and soft parts, the necessity of recognizing its occurrence by means of properly performed autopsies must be strongly emphasized." The classical paper dealing with many phases of the problem was written by Killian in 1930[10] who listed about 200 references and found evidence of brain involvement in about

From the departments of neurology and orthopedics, Temple University Medical School, Philadelphia.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 12, 1951.

one third of the fatal cases. Strauss[11] in 1933 published a review of 124 cases of cerebral form of fat embolism. In two thirds of the cases the symptoms occurred within 24 hours of the fracture. Vance[12] published a comprehensive study of cases seen at routine necropsies at the office of chief medical examiner of New York. Out of 246 cases, fat embolism was considered to be the factor in the fatal outcome of 20 per cent of cases.

From experiences in World War II, important contributions are recorded by Warren[13] who reported on 100 fatal cases, and British investigators[14,15] who emphasized the importance of fat embolism in blast injuries and air raid casualties.

A most instructive panel discussion on fat embolism of the brain and head trauma by such well recognized investigators as Robb-Smith, Allen H. Hunt, Denny-Brown, Dorothy Russell, Greenfield, A. Meyer and others deserves careful study by all who are interested in head trauma.

Robb-Smith stated that with the proper recognition of the condition there will be a decrease in the incidence of delayed shock, traumatic pneumonia, delirium, with a corresponding increase in the number of recovered cases of fat embolism. Also worthy of emphasis is the recent contribution by deGuitterez-Mahoney,[17] purporting to show that cerebral fat embolism is the responsible factor in the mechanism of traumatic cerebral concussion. The author bases his conclusion on a study of four human brains and experimental investigations on dogs. He believes the fat emboli arise directly from the brain. This represents a new approach and an entirely new concept of fat embolism which is deserving of further study. He is among the very few investigators on head trauma who utilized fat stains in frozen sections in his studies.

CLINICAL MATERIAL

This series consists of eight cases of cerebral fat embolism, six fatal and two recovered. Five of the fatal cases came to necropsy. The first three cases were reported individually on previous occasions. The first two represent the acute pathologic picture, and the third, the findings in a case lasting five months. The fourth case exemplified the typical clinical picture. While the pathologic examination was incomplete, frozen sections stained with fat showed the diagnostic feature of fat globules in the lumen of the brain. The fifth case was examined by the coroner's physician and showed no gross intracranial hemorrhage. Microscopic studies were not carried out. The two recovered cases of cerebral fat embolism conformed to the accepted typical picture in the literature.

Case 1.—Summary: Jarring injury to both legs. Two hours later sudden onset of unconsciousness, pyrexia, decerebrate rigidity, tonic fits; coma and death in five days. Pathology: brain edema, petechial hemorrhages, areas of "rarefaction," areas of "coagulation necrosis," and fat globules in the lumen of the vessels.

On July 31, 1934, a white man 19 years of age was forcibly struck in both lower limbs by two gasoline tanks rolling down each side of a collapsed excavation. Both legs were tightly wedged in between the tanks for 20 minutes before he was extricated and brought to the hospital.

Examination disclosed contusions of both lower limbs and mild shock. He was symp-

tom-free for about two hours and was then found unconscious with an abrupt elevation of temperature to 105° F, pulse of 160 per minute, tonic fits and decerebrate rigidty. Rotation of head, manipulations of the extremities, or the slightest noise precipitated tonic seizures which at times were so severe as to raise both lower limbs about six inches above the bed. On the third day petechial hemorrhages appeared over the chest and shoulders. The fundi showed sharply defined, grayish areas in the retina but no choking of discs. A lumbar puncture 12 hours after admission revealed clear fluid and a pressure of 6 mm. of mercury. Another spinal puncture four days later also revealed clear fluid under pressure of 10 mm. of mercury. Roentgen examination of both lower limbs failed to disclose any signs of fracture. Hiccoughs persisted throughout the clinical course. The patient never regained consciousness and expired on the fifth day of illness.

Macroscopic examination: The brain appeared large and edematous. Incision revealed numerous small petechiae gathered in groups throughout the brain.

Microscopic examination: The meninges were markedly dilated, and the blood vessels throughout the pia were dilated and congested, with stasis and clot formation. Outstanding features were 1.) brain edema; 2.) marked decrease in the number of ganglion cells with severe type of cell degeneration leading to liquefaction; 3.) typical ring hemorrhages with central areas of necrosis (figure 1); 4.) numerous areas of "rarefaction" (figure 2), resembling the so-called status spongiosus; 5.) areas of disintegration as a result of "coagulation necrosis" (figure 3), some of these areas showing a definite glial increase; 6.) fat globules in the small vessels often plugging the lumen (figure 4). These various lesions were widely scattered throughout the brain, especially in the subcortex and basal ganglia. These were variable in size and up to the point of being grossly visible.

In view of Dorothy Russell's recent emphasis on the choroid plexuses as the chief site of involvement, the sections were restudied and marked congestion hemorrhage and occlusion of the capillaries with fibrin were observed. In addition there were oval vacuoles in the capillary tuft on hematoxylin and eosin stain which probably represent fat and may therefore be considered highly suggestive of fat embolism, even with routine stain (figure 5).

Comment: In spite of a typical clinical picture of cerebral fat embolism with the diagnostic confirmatory findings of petechiae and ophthalmoscopic signs, the correct diagnosis was entirely overlooked by several consultants for two reasons: 1.) a lack of familiarity with the clinical picture; 2.) an unawareness that fatal fat embolism does occur without fracture of a long bone. Indeed, were it not for the fact that we were absolutely certain there was no direct cranial injury, the condition would have passed as a traumatic encephalopathy. Pathologically, the condition also passed unrecognized. The microscopic diagnoses without fat stains were recorded as brain purpura, traumatic hemorrhagic encephalitis, severe toxic cerebritis. It was only months later, after a restudy of the case with fat stains, that the correct diagnosis was established.

Case 2.—Summary: Fracture of pelvis and femur in elderly person. Free interval of one hour, sudden onset of unconsciousness, decerebrate rigidity. Meningeal hemorrhage suspected, petechiae, lipuria established clinical diagnosis. Pathological findings typical of fat embolism of brain.

A 79 year old white man was struck by an automobile on February 13, 1949 and admitted to the hospital on the orthopedic service. Patient sustained contusions of the forehead, fractures of the pelvis and neck of the right femur. He was mentally clear for one hour and then lapsed into unconsciousness.

Examination revealed an ecchymotic area over the right eye; pupils were equal and reacted to light, rigidity of all the extremities with a positive Babinski sign on the left side, Cheyne-Stokes type of respiration. The following day the patient remained comatose with decerebrate rigidity and intermittent tonic fits. There were radiological changes in the lungs which were interpreted as multiple infarcts. Petechial hemorrhages were discovered first in the conjunctivae and then over the upper thorax. On the third day, the sizzle

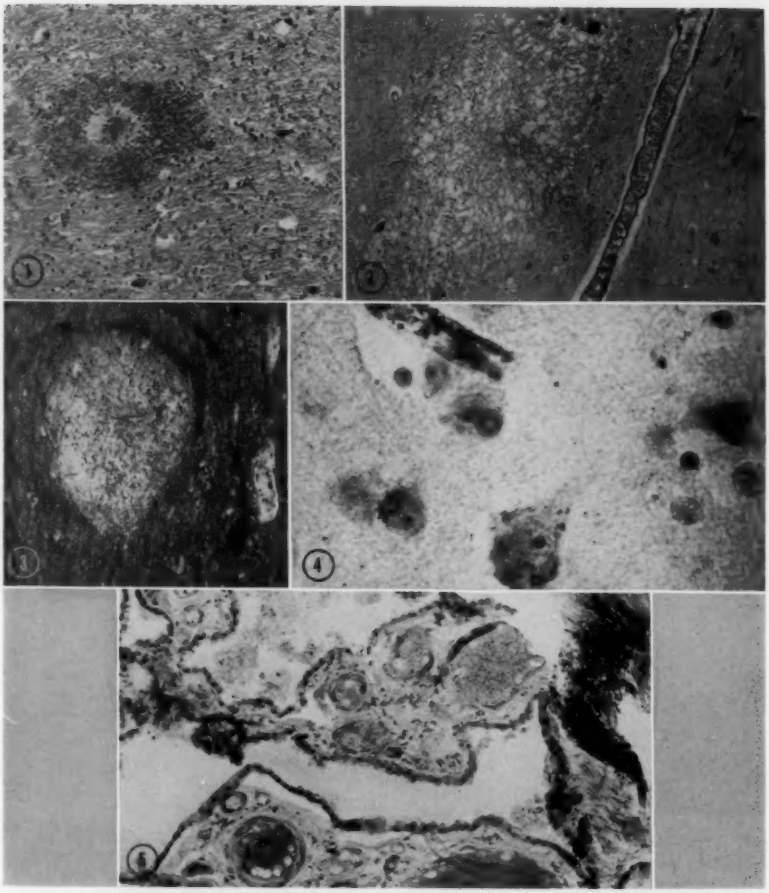


FIG. 1. Ring hemorrhage in brain showing central capillary, zone of necrosis and outer layer of red blood cells. Hematoxylin and eosin stain. FIG. 2. Area of rarefaction in the brain. FIG. 3. Area of degeneration; fat droplets in small vessels in center of arc. Schalarach R. stain. FIG. 4. Fat globules in vessel. Degenerative changes in the ganglion cells. Scarlet-Red stain. FIG. 5. Choroid plexus showing vacuolization of capillary tuft. Hematoxylin and eosin stain.

test for fat in the urine was positive becoming even more strongly positive on the fourth day.

Macroscopic examination: The chief findings in the brain were congestion, edema and multiple scattered petechiae in the subcortex.

Microscopic examination: Fat stains of the lungs and kidneys revealed fat globules in the small vessels. A striking finding in the kidneys was oval vacuoles in the glomerular tuft. A counterpart stained with fat in frozen sections distinctly revealed fat globules at the site

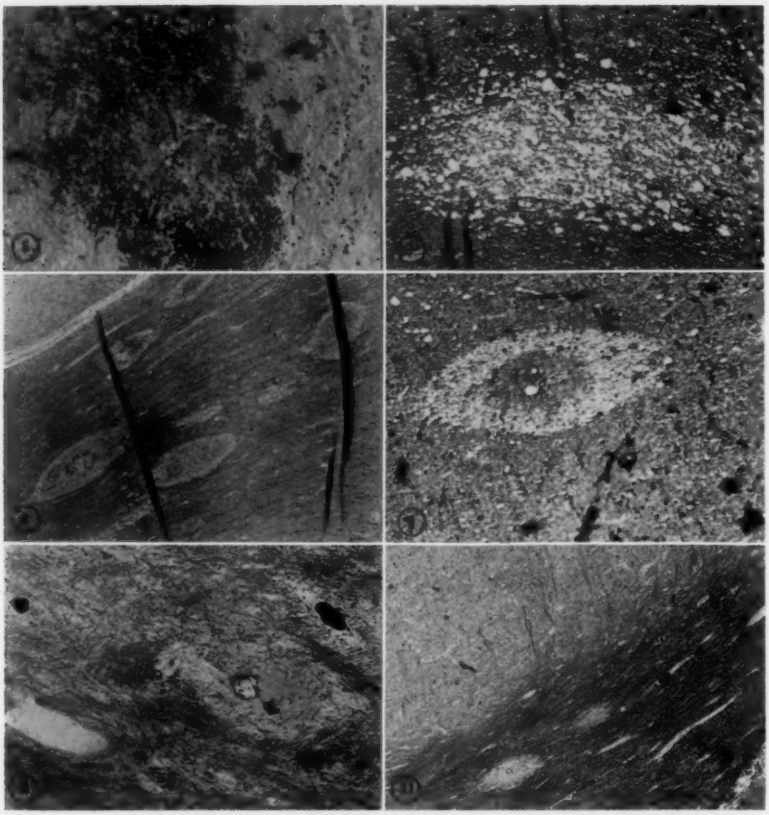
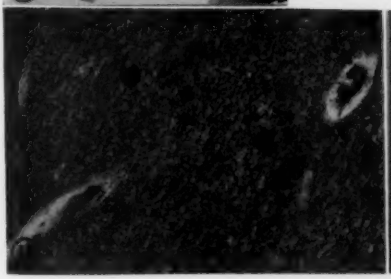


FIG. 6. Typical ring hemorrhage. Hematoxylin and eosin stain. FIG. 7. Area of rarefaction resembling status spongiosus. FIG. 8. Demyelinated areas in subcortex. Myelin sheath stain. FIG. 9. Perivascular demyelination showing central capillary, zone of necrosis and outer meshlike zone. Trichrome stain. FIG. 10. Demyelinated plaques with central capillary plugged with a fat embolus. Various stages of involvement. Fat stain. FIG. 11. Fat stain showing fat in lumen of small vessels and areas of perivascular demyelination.

of the vacuoles. The outstanding histopathologic features in the brain were 1.) petechial hemorrhages (figure 6); 2.) areas of rarefaction (figure 7) and areas of demyelination (figures 8, 9, 10); 3.) fat in lumen of vessels with perivascular demyelination (figure 11). All of these lesions were widespread but chiefly so in the subcortex, basal ganglia, and brain stem.

Comment: The first consideration was to decide whether this was a case of traumatic intracranial hemorrhage which would require emergency craniotomy. In favor of such a diagnosis was the onset of cerebral symptoms following a free interval, with evidence of

FIG. 12. Coronal section showing bilateral necrosis of globus pallidum. Also note dilatation of the ventricles and flattening of edge of caudate nucleus. Myelin sheath stain. FIG. 13. Masses of fatty material in the lumen of two vessels. Scarlet R stain. FIG. 14. Fat globules in vessel of the brain. Scarlet R. stain.



a head trauma by ecchymosis over one eye. The neurosurgical consultant suggested a policy of watchful waiting. The appearance of the petechiae in this case established the diagnosis, and the lipuria was another confirmatory sign. The pathological findings were typical of fat embolism of the brain. There was no gross meningeal or intracerebral hemorrhage.

Case 3.—Summary: Fracture of the femur. Free interval of five days. Operation followed by severe choreoathetoid syndrome of five months' duration. Pathologic findings: bilateral necrosis of the globus pallidum, fat in lumen of the vessels.

A 65 year old woman was admitted to the hospital on June 11, 1945 with a history of having been forcibly thrown to the floor of a trolley car when it came to a sudden stop. Other than local findings of fracture of the femur, examination including laboratory studies was negative. In the hospital the patient appeared to be doing well until the fifth day when she became confused. Appearing bewildered from time to time, she would sit up in bed suddenly, or remain unusually quiet. On the sixth day, under light Avertin (tribromoethanol solution U.S.P.) and nitrous oxide anesthesia, a Thornton plate was applied to the fracture. The patient's pre- and postoperative condition was considered good. Blood pressure at the beginning of the operation was 140 systolic, 90 diastolic; at its completion, 160 systolic, 80 diastolic.

The patient remained somnolent, later becoming restless, delirious and incontinent. Temperature rose to 101° F.; pulse was 100, and respiration 24. The next day she displayed a severe choreoathetoid syndrome with violent movements affecting every part of her body, including the face and tongue. Later ballistic type movements appeared, and the mental picture was that of an organic psychosis. Her condition remained unchanged until she died about five months after the onset of illness.

Pathologic examination: Gross specimen: Atrophy of the inferior surface of the left temporal lobe toward the anterior tip. Coronal sections stained with myelin reveal a dilatation of the ventricular surface of the caudate nucleus, a selective, bilateral demyelination of the globus pallidus in both medial and lateral segments (figure 12). In the substantia nigra there is also a similar, bilateral demyelination running parallel to the pes pedunculi.

"Microscopically, the areas of demyelination show extensive loss of tissue, gitter cell formation and mild gliosis at the edge. The red nuclei show a paucity of cells and those

present are pale and distorted. With sections stained for fat there are small collections of fatty material in some of the arterioles of the cortex; these collections appear chiefly as homogenious masses in the lumen of the vessels (figures 13, 14). However, oval-shaped masses are also present. Near the area of softening in the pallidum is seen a collection of fat about one of the arterioles. Large amounts of fat are also present in the phagocytes as well as in the ganglion cells themselves."

The diagnostic report was "cerebral infarction, probably fat embolism."

Comment: In the case of this elderly patient, there is the following sequence of events: 1.) fracture of the neck of the femur; 2.) free interval of five days; followed by 3.) mental symptoms of confusion and bizarre behavior; 4.) operation under Avertin nitrous anesthesia; 5.) symptoms of diffuse extensive involvement of the brain with a choreoathetotic syndrome.

In spite of the long duration of the condition, there was sufficient evidence of fat in the lumen of the vessels of the brain to indicate the diagnosis of fat embolism. It is quite possible that the patient was beginning to show the signs of mild cerebral fat embolism a day prior to the operation, and that the anesthesia and manipulation greatly aggravated the condition. While the smaller vessels, the capillaries and arterioles, are chiefly involved in fat embolism, various investigators such as Neuburger and Dorothy Russell have shown that the large vessels can also be affected.

Apropos the unusual finding of bilateral necrosis of the globus pallidus, it is interesting to note that a very similar picture was described by A. Meyer[35] in a case of cerebral fat embolism.

Case 4.—Summary: Fracture of femur, free interval followed by delirium, generalized rigidity, tonic, clonic convulsions, pyrexia and dyspnea. Skin petechiae diagnostic. Pathologically, fat globules in lumen of cerebral vessels.

A 61 year old man was admitted to the hospital August 14, 1950 with a history of a fall three days previously. Examination disclosed an intertrochanteric fracture of the left femur. The day following admission there were an abrupt rise in temperature, rapid pulse, dyspnea associated with delirium, confusion, restlessness and stupor. There was generalized extensor rigidity of all extremities, tremors and tonic and clonic convulsions. Spinal puncture showed clear spinal fluid without increased pressure.

A diagnosis of cerebral fat embolism was ventured by the author and substantiated by the sudden appearance of petechial hemorrhages over the thorax and in the conjunctivae. Various studies for detection of fat could not be carried out because the patient's condition deteriorated rapidly, the temperature reached 108° F. and death occurred the third day after admission, i.e., the sixth day following injury.

Necropsy was incomplete. Frozen sections from the brain stained with Scharlach R revealed fat droplets in the small vessels of the brain.

Comment: In this case there is again the typical sequence of events in an elderly individual with fracture of the femur, a free interval followed by pyrexia, and neurologic signs of diffuse overwhelming involvement of the nervous system. The condition was recognized clinically by the typical picture and substantiated by the appearance of the petechia.

Case 5: Fracture of skull with bloody spinal fluid. After free interval of six days, sudden onset of pulmonary and cerebral symptoms. Petechial hemorrhage of diagnostic importance.

A 58 year old man fell from a 12 foot ladder, sustaining a fracture of the left occipital bone and contusions over the occiput and nose. When admitted to the hospital on August 24, 1939, he was in mild shock, slightly confused, and complained of headache. The neurologic examination was negative. Spinal fluid was bloody but not under increased pressure. The patient was mentally clear and progressed satisfactorily for six days when there suddenly developed severe pulmonary symptoms with labored breathing, delirium, confusion and stupor. A medical consultant made the diagnosis of "hypostatic congestion." For the

next week the patient remained in a coma, showed severe tremors and rigidity of the extremities with catatonic manifestations. Nurses and medical attendants discovered skin petechiae over the thorax and conjunctivae. The patient expired seven days after onset of pulmonary cerebral symptoms. Necropsy by coroner's physician was negative for intracranial hemorrhage.

Comment: In spite of the obvious craniocerebral trauma and without fracture of long bone, there was a definite sequence of events justifying the diagnosis of cerebral fat embolism beginning with 1.) the jarring type of trauma; 2.) free interval of six days; 3.) sudden onset of severe pulmonary symptoms, cerebral symptoms of diffuse extensive involvement of the brain; 4.) diagnostic appearance of the skin petechiae.

Finally, it is difficult to conceive of any traumatic brain condition producing such a clinical picture after so prolonged an interval syndrome.

Case 6.—Summary: An elderly woman with fractured femur. Sudden onset of delirium and psychotic behavior after free interval of 48 hours. Fat globules detected in urine.

A white woman aged 78 sustained fracture of the neck of the right femur. For two days after admission to the hospital her condition was good. Suddenly she became deliriour, irrational, stuporous, and died seven days later. With the onset of the mental symptoms there was elevation of temperature, rapid pulse and dyspnea. Examination of the last 5 cc. of a catheterized specimen of urine was positive for fat.

Comment: The sequence of events in this case of a free interval followed by sudden onset of pulmonary cerebral symptoms were quite typical of fat embolism. This type of case occurs rather frequently and is usually diagnosed erroneously as pneumonia, heart failure, or arteriosclerotic dementia.

Case 7.—Summary: Fracture of base of skull and fractures of ulna and mandible. Free interval five days, sudden onset of pyrexia and delirium. Diagnostic skin lesions mistaken for surgical scarlet fever. Recovery without residual symptoms.

A woman aged 22 was struck by an automobile on August 31, 1939 and sustained multiple fractures of the mandible and fracture of the left ulna. She also had signs of a basal skull fracture with bleeding from nose and left ear, and escape of spinal fluid from that ear. After recovery from shock she was well for five days, when there was a sudden elevation in temperature and later a skin eruption which was diagnosed as surgical scarlet fever. She was transferred to the contagious disease hospital on the seventh day following accident.

On admission to the hospital the temperature was 102° F., pulse 120, throat was not injected. A punctiform rash was evident over the anterior thorax. The only positive neurologic sign was a left peripheral facial palsy presumably resulting from the fracture of the left petron. The patient was delirious, restless and lethargic. In the hospital she showed steady improvement. The skin lesions rapidly disappeared within 36 hours. After a week she was oriented for time and place and could answer simple questions. However, in spite of her improved mental state she continued to be incontinent of bladder without apparent discomfort for 12 days. She was discharged about six weeks after admission fully recovered from the cerebral complication. The only positive sign was peripheral facial palsy.

Comment: The fact that this patient sustained a fracture of the skull, an interval syndrome followed by cerebral signs brought up the question whether the entire clinical picture was due to a traumatic encephalopathy, especially intracranial hemorrhage. However, the long free interval of five days, the absence of increased intracranial pressure, no pupillary inequality, were against a diagnosis of a dural hemorrhage. On the other hand, there was a typical sequence of events with an interval syndrome of five days' duration. The profusion of skin petechiae was erroneously diagnosed as surgical scarlet fever.

Case 8.—Summary: Multiple fracture of the tibia, fibula, free interval of 18 hours. Sudden onset of rigidity, traumatic meningeal hemorrhage suspected, petechial hemorrhages established diagnosis of fat embolism.

A colored man aged 31 years was admitted to the hospital April 19, 1950 with fractures of the femur, left tibia and fibula, and multiple contusions and abrasions. There was a vague history of a period of unconsciousness for about one half hour prior to admission. In the hospital he was conscious; blood pressure was 120/76. He appeared to be quite well in spite of injuries for 18 hours when he suddenly became confused, irrational and lethargic. Lumbar puncture revealed 200 mm. of mercury pressure; the fluid was clear.

When examined two days later he was in coma; the right arm was rigid and held strongly flexed at the elbow, while the right leg was in extensor rigidity. The left upper limb was flaccid; the left leg in a cast. There was a positive Babinski sign on the right. Turning the head caused an intensification of rigidity with tonic spasms throughout the entire body. There were typical petechial hemorrhages in the lower conjunctivae of each eye and over the upper thorax. This was first discovered by the nurses who were alerted to search for such lesions. The following day the patient appeared somewhat improved. Rigidity in the extremities was less marked. The skin petechiae in the lower conjunctivae were still striking and there were numerous petechiae hemorrhages over the upper anterior chest and shoulder. These occurred in groups of five to ten; some of the skin lesions had begun to fade. The patient continued to improve and within a week after the onset he was able to answer simple questions. In spite of the superficially clear sensorium he remained incontinent for about two weeks. One month after admission to hospital patient returned to his normal mental level fully recovered from the neurologic complication.

Comment: This patient presents a dramatic illustration of a recovered case of cerebral fat embolism. Again, the typical sequence of events could be followed beginning with a severe jarring type of trauma with multiple fractures and contusions, a free interval followed by pyrexia, rapid respiration, and neurologic signs of a diffuse extensive involvement of the brain. In this case the diagnosis of a massive dural hemorrhage had to be considered. Indeed, an emergency craniotomy was contemplated. However, there were no signs of increased intracranial pressure and no pupillary changes. The appearance of the skin petechiae tied in quite well with the diagnosis of cerebral fat embolism.

ETIOLOGY AND INCIDENCE

The most common conditions contributing to fat embolism are trauma to the osseous structures especially fracture of a long bone; orthopedic procedures; jarring of the skeleton with or without fracture; surgical operations on the viscera; severe burns; and injury and crushing of the subcutaneous and intermuscular fat. Of great significance are two reports of fatal cases resulting from Triazol[18] and electroconvulsive therapy.[19] Other causes have been mentioned such as therapeutic injections of oily solutions, massive arsenotherapy, poisoning from phosphorus, carbon monoxide, ammonia and other alkalies.

Osteoporotic bones in old people and atrophic bones in children caused by disuse are particularly susceptible to this complication.

Attention should be called to the reports of Bissel[20] in 1916 and Sutton[21] in 1922, both papers from the necropsy service of the Mayo Clinic. Both authors clearly point out that postoperative fatalities following various operations on the viscera including the brain and spinal cord, which are usually diagnosed clinically as postoperative shock, proved to be instances of fat embolism. These provocative reports have not received the careful study they merit from surgeons and pathologists.

The traumatic situation that is most likely to give rise to fat embolism results from violent jarring of the skeleton with multiple bruises. This type of

TABLE 1

FATAL CASES OF FAT EMBOLISM

Sex & Age	*Trauma*	*Free Interval*	*Clinical Picture*	*Confirmatory Signs*	*Survival*	*Remarks*
M 19	Jarring, crushing both legs, multiple bruises, no fracture	2 hours	Coma, tonic fits, decer. rigidity, Temp. 105° F., Sp. fluid clear	Petechiae, chest, Grayish areas in retina (3rd day)	5½ days	Ring hemorrhages, areas of rarefaction, fat in lumen of vessels
M 79	Struck by auto, Fractured pelvis, femur; ecchymosis forehead	1 hour	Delirium, coma, tonic fits, decer. rigidity, Temp. 103° F., Sp. fluid clear	Petechiae, chest, conjunctivae (2nd day) Lipuria (3rd day)	4 days	Typical findings as case 1
F 65	Fall in trolley car. Fractured neck of femur	5 days, operation on 6th day	Delirium, choreoathetosis, Temp. 101° F.		5½ months	Bilateral necrosis of globus pallidum, fat in vessels
M 61	Fall on floor. fractured femur	4 days	Delirium, coma, tonic fits, decer. rigidity, Temp. 108° F., Sp. fluid clear	Petechiae, chest, conjunctiva (24 hours)	6 days	Fat globules in lumen of cerebral vessels
M 58	Fall 12 ft. Fractured occiput, contusions	5 days	Acute pulm. edema, delirium, stupor, rigidity and catatonic manifestations	Petechiae, chest, conjunctiva (5 days); Temp. 103° F.	7 days	Coroner's case. No gross intracranial hemorrhage
F 78	Fall on pavement, fractured femur	2 days	Acute pulm. edema, restless, delirium, coma	Lipuria (3rd day)		No autopsy

RECOVERED CASES

Sex & Age	*Trauma*	*Free Interval*	*Clinical Picture*	*Petechial Hemorrhages*	*Remarks*
F 22	Struck by auto; fractured mandible, ulna, base of skull, base of spine	5 days	Restless delirium, lethargy	Chest (1 day) sent to contagious disease hospital, lesions mistaken for scarlet fever; Temp. 103° F.	Progressive improvement after 1 week; incontinence bladder for 14 days; recovery in 6 weeks
M 31	Auto collision; fractured tibia, fibula	18 hours	Delirium, coma, decer. rigidity; spinal fluid clear	Conjunctivae chest (1st day); Temp. 101° F.	Progressive improvement after 4th day; incontinence bladder 12 days; complete recovery in 1 month

trauma which forms the bulk of traffic casualties of everyday experience also causes cerebral concussion and other craniocerebral injuries. The same jarring factor is present in blast concussion and air raid casualties. Jarring or concussion of the skeleton without fracture of a long bone as exemplified in case 1 has been stressed as an important etiological factor in fat embolism for about 75 years by leading investigators and has been reviewed in a previous communication.[22] The frequent occurrence of fat embolism in blast injuries, air raid casualties and battle wounds was well demonstrated by British and American investigators who reported large series of cases.

Figures vary greatly as to the incidence of fat embolism. Case 2 represents the only case so diagnosed at the Philadelphia General Hospital. Up to 1938 when our first case was reported, there was no record of a diagnosis of this condition at Temple University Hospital. Since 1944, there have been

seven cases recorded in the orthopedic service which represents almost all of the cerebral pulmonary complications that took place during this period. With a growing familiarity of the condition more cases have been recognized as, for example, three cases in 1950 on the same service. During the last war Wilson and Salisbury[23] reported eight cases in a thousand battle injuries, six of which were fatal. Robb-Smith[14] in a study of 115 consecutive necropsy cases found extensive fat embolism in 41 cases and in 29 it was responsible for the fatal outcome. He concluded that pulmonary embolism was an important factor in death from bombings. Wakely[24] found 40 per cent of fat embolism in fatally burned cases. While a number of investigators have reported varying degrees of pulmonary fat embolism in many non-traumatic situations, fat globules in the lumen of the vessels of the brain invariably indicates trauma. The occurrence of fat embolic lesions in sickle cell disease is worthy of emphasis.

MECHANISM AND TRANSPORTATION OF FAT

The essential feature in fat embolism is that there are fat globules in the blood of sufficient size to obstruct the small blood vessels and induce multiple infarcts. This must be distinguished from the lipemia of diabetes in which the fat is so finely emulsified that globules pass easily through the smallest capillaries.

There is considerable disagreement as to the source of fatty material and its mode of entry into the circulation. The most acceptable explanation is that the chief source is injured bone. The fat globules are liberated and are forced under pressure into the open haversian veins While this mechanism may be true for some cases of fracture, it certainly does not explain case 1, a relatively minor injury, and those cases following orthopedic manipulations. Furthermore, it has been claimed by some observers that there is not enough fat in any long bone of the body to cause death even if all of it should enter the circulation. Lehman and Moore[25] and other investigators claim that the absorption into the blood stream of products of protein decomposition at the site of trauma causes a change in the physiochemical condition of normal blood fat from the emulsified state to large globules of fat sufficient to produce anoxemic foci. Robb-Smith[14] believes that traumatized tissues may release a lipoproteinase which may alter the blood chemistry and cause fat emboli.

Much experimental work has been done to determine the mode of transportation of fat. Busch[26] demonstrated that olive oil colored by cinnabar, when injected into the medullary cavity of the tibia of a rabbit, could be traced into the haversian canals, quickly obtained from inferior vena cava and subsequently found in the pulmonary tissue.

Once fat enters the circulation it is carried first along the great veins to the right side of the heart where it mixes with the blood and increases its viscosity. It is then carried to the lungs where it occludes the capillaries, interferes with normal oxygen exchange and blocks the smaller capillaries.

This causes congestion, edema, hemorrhages and small patches of inflammation which interfere with the pulmonary circulation, and hence produces symptoms of dyspnea, cough, cyanosis, giving rise to the classical pulmonary type of fat embolism. Obstruction to the pulmonary flow causes back pressure and dilatation of the right side of the heart. The embolic fat may occlude the pulmonary artery and result in immediate death.

The fat enters the systemic circulation either through a patent foramen ovale or the fat globules are forced through the capillaries into the systemic circulation by increasing pressure in the lungs. Since the cerebral involvement dominates the clinical picture invasion of the greater circulation has been referred to as cerebral fat embolism.

The disposal of fat is believed to be accomplished by phagocytosis; it is excreted in the kidney and to a lesser extent in the bile. Experimental work indicates that fat globules begin to dissolve in the blood stream after 48 hours and may disappear in three days.

CLINICAL PICTURE

The clinical recognition of fat embolism differs according to whether the fat is held in the lungs or enters the systemic circulation. Hence two main clinical types have been described: 1.) a pulmonary type with symptoms of acute pulmonary edema; 2.) cerebral fat embolism, so designated because of the predominance of brain involvement. A cardiac type has also been described by Warthin.[9] While the systemic fat embolism is often accompanied by pulmonary symptoms, the latter symptoms have been absent in about one third of the cases reported by Strauss.[11]

The clinical picture of cerebral fat embolism follows a characteristic pattern which may be readily recognized by a definite sequence of events. The most important diagnostic feature is the so-called free interval during which the patient is relatively comfortable and free from complications. This period is usually two to three days but it can range from 30 minutes to nine days. In our series, the shortest period was one hour and the longest, six days.

The next feature is a sudden lapse into unconsciousness accompanied by pyrexia. In several of our patients this phase was preceded by pulmonary symptoms, dyspnea, cough, frothy sputum. Restlessness, tachycardia, precordial pains have all been described as premonitory symptoms. The cerebral manifestations vary from insomnia, delirium, disorientation, psychotic reactions, increasing stupor, clonic and tonic convulsions, rigidity including the decerebrate type. Rarely there are mild focal signs with positive Babinski. The decerebrate picture was present in five of our eight cases and in three instances was associated with hyperthermia. With a deepening of the coma the irritative signs disappear; the pupillary and corneal reflexes are lost; rigidity is replaced by flaccidity, and paralysis of the sphincters supervenes. Death is usually heralded by rapid respiration of the Cheyne-Stokes type. Signs of cerebral compression are absent; the spinal fluid does not show increased intracranial pressure.

With this clinical picture, the sudden appearance of petechial hemorrhages in the skin has been considered diagnostic and even pathognomonic of cerebral fat embolism by Neuburger and other investigators. These dermal lesions, which have proven to be fat infarcts, usually appear the third day of the illness but may occur within the first 24 hours. They are usually located over the upper part of the chest, shoulders and mucous membranes, at times only in the conjunctivae. They do not disappear on pressure and usually persist for about 48 hours. Petechiae occurred in six of the cases presented here.

Another invaluable diagnostic sign during this period is the ophthalmoscopic observation of fat globules in the retinal vessels,[27,28] hemorrhages, or the pale sharply marginated areas in the retina.[29] Lillie[28] considered the appearance of the oval masses of fat in the retinal vessels as diagnostic and distinguished this picture from the fatty changes in the vessels occurring in the lipemia of diabetes. Emphasizing the practical diagnostic value of these retinal changes is the recent report by Evans[30] of a recovered case of cerebral fat embolism in which the diagnosis was established by ophthalmoscopic findings of diffuse edema of the retina, areas of crescentic pallor and subhyaloid hemorrhages.

Other confirmatory signs are fat globules and fat granule cells in the sputum (Warthin) and detection of fat globules in the urine. In examining the urine the bladder must be completely emptied usually by catheter and the last 3 to 5 cc. of urine examined. In this connection the sizzle test has proven of distinct value. A drop of urine is taken up in a platinum loop and held over a gas flame. If fat is present a sizzling and popping sound is heard (Scuderi[31]). While the diagnostic significance of lipuria has given rise to considerable discussion, Strauss,[11] Elting and Martin[32] and other investigators have insisted it is diagnostic even in those instances where the clinical picture of fat embolism is not fully developed.

Scuderi[33] has recommended qualitative dark field examination of the blood as a great aid in diagnosis. Roentgen examination of the chest based at first on experimental work has become a definite diagnostic aid in pulmonary fat embolism. Recently, Harris[34] and his coworkers emphasized a profound fall in the hemoglobin as a significant new sign in fat embolism.

DIAGNOSIS

A prerequisite for the recognition of cerebral fat embolism is a familiarity with the clinical features, and better still, becoming "fat embolism minded." The diagnosis should be considered in every instance of sudden onset of cerebral symptoms following trauma and other known etiological factors. To be emphasized is the fact that it can occur without a fracture and should not be overlooked in instances of head trauma.

The condition should be differentiated from shock, circulatory collapse, uremia, diabetic coma, bronchopneumonia, delirium tremens, cerebral concussion and intracranial hemorrhage. Some observers have insisted that shock

is nothing more than an expression of fat embolism. While in some instances this concept may appear to hold true, in other instances the two conditions may be present and yet remain distinct. It has been pointed out that high grade fat embolism can occur without symptoms of shock. While in the latter the temperature is subnormal, the peripheral veins collapsed, the sensorium clear, in fat embolism there is more likelihood of pyrexia, mental changes, and no difficulty in venipuncture.

There seems to be some confusion between fat embolism and pulmonary or cerebral embolism due to clot formation following some surgical procedure. Not infrequently the clinical picture in both conditions is similar; sudden death can take place in either case. This differential diagnosis came up in case 2. The appearance of the petechiae and lipuria established the diagnosis of fat embolism.

In analyzing our cases one is impressed with the similarity of the clinical picture with craniocerebral injury, a fact emphasized in a previous paper.[22] The violent jarring type of trauma with multiple bruises, which is the most likely one to cause fat embolism, usually causes cerebral concussion and other craniocerebral injuries as well as fracture of bones. The interval syndrome is a characteristic feature in both fat embolism and traumatic dural hemorrhage. In those cases of head trauma with prolonged unconsciousness, fat embolism may be readily overlooked because of the absence of the diagnostic feature, the free interval. Restless delirium and stupor may result from cerebral contusion or fat embolism, or a combination of both conditions. Hyperthermia and decerebrate rigidity which occurred in several of our cases can also occur in cases of head injury. In the latter they represent ominous signs of a massive dural hemorrhage with compression of the brain stem.

In the early phases of several of our cases it was difficult to exclude an extradural or subdural hemorrhage. Fortunately, the early appearance of the skin petechiae helped to establish the diagnosis of fat embolism. Without such aids in diagnosis a careful analysis of each individual case will be necessary. In favor of dural hemorrhage are fluctuations in the state of consciousness, unilateral dilatation of the pupil, signs of increased intracranial pressure and progressive hemiparesis. In suspected cases of epidural hemorrhage when the decision to operate is imperative, the "woodpecker" type of surgery recommended by Walker would be justified even when fat embolism is strongly suspected.

From the aforementioned data as well as evidence in the literature, it seems logical to suggest that every case of head trauma with unusual cerebral symptoms should call for the sizzle test for fat in the urine. In addition, there should be a diligent search for petechiae in the conjunctivae and skin on the part of attending nurses as well as physicians, and last but not least, repeated ophthalmoscopic examinations for embolic lesions as a routine in the management of such cases.

HISTOPATHOLOGIC CHANGES

The characteristic pathologic lesions in cerebral fat embolism are well illustrated in the first two cases and follow the classical description. The first case clearly demonstrates that without the use of fat stains in frozen sections even a typical picture of fat embolism can be overlooked.

The first two cases represent the usual pathologic lesions in patients with a survival period up to five days. The striking feature in the second case was the scattered diffusely marginated areas of demyelination. In some of the lesions there was a perivascular demyelination with a central capillary, at times completely occluded by fat, surrounded by a layer of fibrin and then a thin layer of mesh-like substance. These probably represent anemic infarcts.

The pathologic findings in the third case are presented as evidence of chronic cerebral fat embolism of five months' duration. The striking feature of bilateral selective necrosis of the globus pallidum in this case was also reported as an unusual finding in a case of cerebral fat embolism by Meyer.[35]

Winkelman[36] has demonstrated that the various lesions in cerebral fat embolism result from plugging of vessels affected. Neuburger[37] stated that variation in the collateral capillary circulation is rich, the gray matter is invaded profusely with fat emboli and yet there result only small paled areas or areas of necrosis, the "rarefied areas" and petechial hemorrhages. Although the smaller capillaries are usually affected, recent reports by British investigators Meyer[35] and Dorothy Russell[38] emphasize that the medium and larger vessels can also be implicated. Dorothy Russell stresses the choroid plexuses as the chief site of fat embolic lesions. Study of our first case showed a marked involvement of the choroid plexuses and in addition oval vacuoles in the capillary tufts on hematoxylin and eosin stain which might be considered diagnostic of fat embolism even in routine preparations.

Whereas the visualization of fat emboli in the lumen of the vessels is of diagnostic significance, its absence would not exclude the diagnosis. Kroskloss[39] has shown that fat may be concentrated in any organ, thus sections from several viscera such as the heart, lungs, kidneys, pancreas, adrenals and liver should also be examined for fat.

The two types of pathologic lesions stressed in the literature are petechial hemorrhages and "rarefied areas," both of which are chiefly located in the subcortex. Vance and others have considered these hemorrhages as minute hemorrhagic infarcts caused by fat emboli. They usually appear after the condition has existed for more than two days, although they have been known to occur as early as 24 hours and, in many instances, have been entirely wanting. The so-called ring hemorrhage has a characteristic appearance; in the center there is usually found one or more fat-filled vessels surrounded by a circular necrotic zone and around this a circular zone of extravasated red blood cells.

The "'rarefied areas" are translucent, mesh-like, resemble status spongiosus and occur in the vicinity where the blood vessels are filled with fat. Vance[12]

believes these areas are due to a sudden and intense destruction of medullated sheaths due to anemic necrosis with preservation of the axis cylinders, while at the same time lymphatic fluid pours in from the surrounding tissues and widens the meshes. The lesion is considered as an anemic infarct in the brain. Greenfield[40] points out that the well defined areas of destruction of neurones and myelin in cerebral fat embolism are quite unlike those seen in any other condition—that "these appearances should therefore make it possible to recognize fat necrosis by ordinary tissue stains even in non-hemorrhagic cases." Scheinker[41] considers the diffuse scattered areas of demyelination a most constant and striking finding and points out the similarity of these lesions to multiple sclerosis.

Attention should be called to the close similarity and almost identical lesions in cerebral fat embolism and certain cases of traumatic encephalopathy. Without the use of specific fat stains, our first two cases showed the histopathologic findings that are described in the literature as characteristic of severe concussion under such terms as "traumatic encephalitis" or "traumatic multiple hemorrhages." Rand and Courville[42] pointed out that the petechial hemorrhages in head trauma may be due to either fat embolism or changes in the cerebrospinal fluid. The work of de Guitterez-Mahoney attempted to prove that traumatic cerebral concussion is due to cerebral fat embolism. Noteworthy, too, are the reports by Vance[12] and Dorothy Russell[38] of extensive cerebral fat embolism in cases of severe head trauma.

PROGNOSIS

Since the literature deals mainly with the reports of fatalities and the recovered cases are seldom recognized, the mortality is high. However, there are a number of reports of recovery. Dahl[43] reports three; Benestadt[44] three; Whitaker[45] two; and Harris et al.[34] six cases. In this paper two recovered cases are reported, and there are six recovered cases on record at Temple University Hospital. While in most of the recorded cases complete recovery has taken place, there is suggestive evidence that residual symptoms and signs are possible. In this regard, the report by Alan H. Hunt[46] of a patient with residual symptoms of headache, sleep disturbances, two years following recovery from fat embolism is pertinent.

MEDICOLEGAL ASPECTS

This aspect of the subject appears to have received the least attention in the literature. As mentioned previously, Warthin emphasized this factor in 1913 by stating: "fatal cases of fatty embolism form the common accidents of our large cities and are diagnosed everyday as shock, coma, apoplexy, alcoholism, concussion, 'bad heart,' etc. There should be further study and investigation of certain medicolegal aspects of fatty embolism." Little need be added to this statement other than to point up the alarming increase in traffic accidents since 1913.

Since almost all of the fatal traumatic cases come under the control of the coroner's office, an ideal opportunity is provided to obtain invaluable data concerning the relationship between trauma and fat embolism, which should prove of practical importance. Too often the coroner's physician is merely interested in the gross findings which do not necessarily disclose the true pathologic picture.

TREATMENT

In the literature great stress is placed on prophylactic measures to reduce incidence of fat embolism. These include the avoidance of unnecessary or rough handling of fracture cases; immediate splinting and early reduction of all fractures and other orthopedic measures. With regard to specific therapy, numerous drugs have been recommended. Intravenous infusion of sodium carbonate to saponify the fat has not proved of value in practice. Other infusions with Ringer's solution, glucose and physiologic saline solutions have also been proposed by different authors. Rappert[47] has advocated the use of intravenous administration of sodium desoxycholate. Robb-Smith[14] used this treatment in a case of pulmonary fat embolism and found that while the pulmonary symptoms improved cerebral fat embolism developed with a fatal outcome. The Drinker apparatus has been used with good results in tiding the patient over the dangerous period. High concentration of oxygen administered by a closed B.L.B. mask has been highly recommended. For the most part the treatment is symptomatic. If the patient survives to the sixth day after onset of cerebral symptoms the chances for recovery are good.

SUMMARY AND CONCLUSIONS

From a review of the literature it would appear that cerebral fat embolism is a specific entity of rather frequent occurrence which is often overlooked both clinically and pathologically. The cases presented here graphically demonstrate that the condition can be recognized clinically. It can occur from relatively minor injury without fracture of a long bone, or from skull fracture alone, and recovery is possible even when the clinical picture is fully developed. While fracture of a long bone has always been identified with fat embolism, attention is called to other etiologc factors equally as important. Of particular interest is the report of fatal cases resulting from "shock" therapy. Apart from providing an explanation for fatalities in such cases, frequently ascribed to other causes, it offers a logical mechanism for the organic cerebral syndromes and the frequent memory deficit following electroshock therapy.

In this paper great emphasis is placed on the similarity of the clinicopathologic picture of cerebral fat embolism with craniocerebral trauma. It is suggested that the clinical picture in cases of head trauma is frequently due to fat embolism. The violent jarring type of trauma with multiple bruises which is most likely to cause fat embolism also results in craniocerebral trauma.

Evidence is presented to warrant the suggestion that cases of head trauma be considered in the same category as any other form of trauma. A diligent search for the confirmatory signs of fat embolism should be included in the management of such cases.

Pathologically, cases of head trauma should include fat stains in frozen sections.

The clinical features consist of a lucid interval, a sudden development of rapid pulse, pyrexia and dyspnea; various neurologic symptoms and signs indicating diffuse extensive involvement, especially that of decerebrate rigidity. Cutaneous and conjunctival petechial hemorrhages are particularly stressed as an important diagnostic feature.

The histopathologic lesions are due to plugging of blood vessels and consist of edema, congestion, ring hemorrhages, areas of rarefaction, demyelinated areas, and globules of fat in the blood vessels. The visualization of oval vacuoles in the choroid plexuses and in the glomeruli of the kidney may be diagnostic of fat embolism even with routine stains.

The medicolegal implications in fat embolism are significant and point to a need for re-evaluation in connection with the posttraumatic neuropsychiatric syndromes.

The important role of fat embolism in bombings and air raid casualties demonstrated during World War II, deserves special attention and is a timely subject for research from the standpoint of management.

Finally, the proposed hypothesis that alteration in the blood chemistry itself may be the source of fat globules, as exemplified in such non-traumatic conditions as alkali poisoning and sickle cell disease, is provocative. Could not this physicochemical instability be one of the factors in the mechanism of some of the unknown clinical demyelinating syndromes of neurology?

I am indebted to Dr. J. R. Moore for his encouragement and the opportunity to study the clinical cases on the orthopedic service. I wish to thank Dr. L. Jordan for his contribution in the study of case 2 and express appreciation to Coroner Joseph Ominsky for his cooperation in releasing the brain for microscopic study.

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The diagnostic significance of convulsions depends on their character. They may be general or they may be partial, either in extent or in commencement. General convulsions constitute a "diffuse" symptom. They are often due to a diffuse and widespread morbid process, inflammatory of degenerative disease away from the motor centres or to general increase of intracranial pressure.

—Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Serial Electroencephalography in Vascular Lesions of the Brain

E. Roseman, M.D.,
Richard P. Schmidt, M.D. and Eldon L. Foltz, M.D.

THE early years of clinical electroencephalography were devoted to the accumulation of statistical data in such conditions as the epilepsies, brain tumors, head injuries, vascular lesions of the brain, as well as data on normal subjects. This material, although basic and important diagnostically, gave but little hint as to the underlying pathophysiologic changes which the brain undergoes following cerebral damage. A single electroencephalogram merely indicates the electrical activity of the brain at that particular time. Since all disease is a moving process, it would seem desirable to attempt to correlate the dynamic clinical alterations with serial variations in the electroencephalogram. This correlation of the electroencephalographic changes in disease or trauma with the altering clinical picture is defined as dynamic electroencephalography.

Elsewhere it has been shown that the electroencephalograph can be used serially (dynamically) in the accumulation of diagnostic and prognostic data in trauma to the brain,[1] encephalopathies,[2] and in such vascular diseases of the brain as aneurysms.[3] But dynamic electroencephalography need not be so confining. It can be used to understand better many conditions involving the brain directly or indirectly, whether they be of a vascular, neoplastic, degenerative, traumatic or congenital nature. Frequently the lack of change in the electroencephalogram is of as great importance as its serial alterations.

GENERAL PRINCIPLES OF DYNAMIC ELECTROENCEPHALOGRAPHY

1. *Presence of delta (slow) wave activity.* Delta activity in this study is confined to the frequency range of ½ to 5 cycles per second. The presence of delta activity per se in the electroencephalogram has no significant diagnostic value. It is the non-specific response electrically of the cortex to injury. This is true regardless whether this injury be of a traumatic (external) nature or spontaneous (e.g., neoplasm, vascular lesions, encephalopathies, etc.). Delta activity indicates injured or diseased neurones, not dead nerve cells. To record

From the sections of neurology, neurosurgery and electroencephalography, University of Louisville School of Medicine, the Louisville General Hospital, and the Veterans Administration Hospital, Louisville, Kentucky.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 13, 1951.

delta activity by clinical electroencephalography, the anatomic or physiologic alterations must be near the cortex. Isolated deep lesions usually do not produce notable slow activity as recorded from scalp electrodes.

2. *Dynamic changes in delta activity.* Delta activity is seldom, if ever, static. It either becomes worse (slower and higher voltage) or disappears. In regressive lesions of the brain, e.g., trauma, thrombosis, vasospasm, it resolves. In progressive cerebral disturbances, e.g., tumors, the slow activity increases.

In the interpretation of changes of delta activity, several factors need to be considered, including: (a) whether it is continuous or intermittent, (b) location and distribution, (c) duration of its presence, and (d) with what it is replaced. Wide spread and long persisting delta activity (weeks to months) indicates severe injury and increases the probability of permanent sequelae. A well defined, circumscribed delta focus usually indicates a benign lesion. Diffuse delta activity may point to a more malignant disturbance. Also, if the delta activity disappears rapidly, one is usually dealing with a more benign lesion.

In regressive lesions of the brain, delta activity seldom persists more than three months. In the more severe cerebral vascular disturbances the curve of delta evanescence would be somewhat as follows: Rapid resolution in a more or less geometric ratio for the first seven to 14 days and a slower regression in an arithmetic ratio for the next eight to ten or more weeks. This curve of recovery in such lesions is well known clinically. The electroencephalographic changes (disappearance of delta activity) frequently precede or may accompany the clinical changes.

In the first days subsequent to cerebral injury it may be difficult to assess adequately the exact nidus of abnormality. This is due to such additional pathophysiologic alterations as associated vasospasm or edema. The former seems to be particularly notable during the first three postictal days and the latter may endure as long as ten to 14 days. Both of these phenomena not only produce delta activity, but may initiate diffuse or remote effects. Serial electroencephalography can help in the resolution of such clinical and electroencephalographic artifacts. It is in the study of these phenomena as well as the interpretation of vascular occlusive lesions of the brain that dynamic electroencephalography has its greatest value.

3. *Absence of delta activity.* The absence of delta activity following brain damage may be of as signal importance as its presence. As noted above, delta waves usually indicate injury to the electroencephalographically accessible cortex. Presence of severe neurologic sequelae with little or no slow activity usually indicates a deep hemispheric or brain stem lesion. Thus, for example, a small surface thrombotic lesion with a transient monoparesis may produce initially a well defined delta wave focus. On the other hand an internal capsule or brain stem lesion can produce a severe and persistent hemiplegia and no delta activity. Using this as a simple example one may use dynamic electro-

encephalography as a prognostic tool. Hence, the presence of severe neurologic signs (e.g., hemiplegia) and delta activity would indicate a guarded prognosis. As long as slow activity is present anatomical and clinical improvement is possible. In the absence of delta activity a poor recovery program is usually indicated for one or the other of two reasons: (a) no further anatomic or physiologic recovery is possible and (b) the lesion is so deep that important and irreversible anatomic destruction of the final common pathways has taken place.

4. *Time as a factor in delta activity.* It has already been indicated in 1, 2 and 3 above, that time is the all important parameter in the consideration of the significance of delta activity. To summate, it might be stated that delta activity (a) when present, indicates underlying cortical damage, (b) appears immediately after cortical damage, (c) remains as long as anatomic changes occur and (d) when it disappears, usually heralds maximal anatomic and physiologic recovery.

5. *Replacement of delta activity.* Once the delta activity has resolved, the electroencephalogram does not remain stationary. One, or possibly two, important and hitherto not emphasized electroencephalographic findings present themselves: (a) amplitude asymmetry has been a constant phenomenon in regressive hemispheric lesions. Initially, with or without focal slow activity, ipsilateral decrease of alpha or background activity is seen. This persists for two to three weeks or until the delta focus begins to clear. This initial amplitude reduction is seen best in the homolateral temporal and occipital areas and is the permanent sequel of brain damage. However, this amplitude asymmetry may fluctuate two to three or more times before reaching its final ipsilateral reduction. In no case do all these alterations in voltage take more than three to six months. (b) It has been shown that following cortical injury up to 40 per cent of cases develop electroencephalographic epileptogenic foci.[1] The latter do not appear until the delta foci have resolved, but may make their appearance concurrently with the amplitude alterations.

In summary, it may be said that in using dynamic electroencephalography, the presence, site and duration of delta activity is all important, particularly in the study of vascular lesions of the brain. In the case of intracranial aneurysms one may, by this method, gain information on: (1) lateralization, (2) localization, (3) phenomena associated with rupture, e.g., vasospasm, thrombosis, (4) effect of ligation of the carotid arteries in the neck, (5) effect of direct surgical attack on the aneurysm, and (6) end results.[3]

In the present study the use of dynamic electroencephalography in the phenomena of cerebral thrombosis, embolus, vasospasm and edema is emphasized.

Previous reports of the electroencephalogram in cerebral vascular disease have been concerned with statistical analyses of patterns without particular reference to the factor of time and the use of serial records as a prognostic and differential diagnostic tool. Dynamic changes in amplitude asymmetries

have not been described in these conditions.

Schlesinger and Strauss,[4] in comparing the use of pneumoencephalography with electroencephalography in brain tumors, stated, "Fortunately, cerebrovascular disease is only rarely associated with the type of records most frequently produced by hemispheric tumors." The validity of such a statement would seem to depend upon the factors of time and localization. Thus, a well defined delta focus may be present immediately following a vascular insult but disappears with time. If records are taken several months after ictus a high incidence of delta activity cannot be expected. Identical types of foci may be present initially but it is in the dynamic changes that differential diagnostic information is obtained.

Strauss and Greenstein[5] reported on the electroencephalographic findings in 95 patients with cerebral vascular disease. For most patients a single electroencephalogram was made, ranging in time from one day to one year following ictus. They found a relatively small proportion of focal electroencephalographic abnormalities in cases of vascular occlusion. In cerebral neoplasm, 119 of 162 cases had delta foci as compared to eight of 95 cases of vascular disease. Critically, it may be stated again that the factor of time in relation to delta foci and focal amplitude asymmetries were not considered.

Cohn, Raines, Mulder and Newman[6] reported on electroencephalographic and neuropathologic correlations in 130 cases of which 104 were classified as thrombosis, embolus or hemorrhage. Although serial studies were not emphasized, they noted prominent focal slow wave activity in superficial lesions and its absence in deep subcortical lesions.

Epstein, Lennox and Noto,[7] in a study of experimental occlusion of the middle cerebral artery in dogs, correlated electroencephalographic abnormalities with time and with the pathologic extent of the lesions produced. In large lesions prominent slow activity was seen at the boundaries with decreased electrical activity in the mid zone. Duration of slow activity varied with the size of the lesion. Depression of sleep spindles ipsilateral to the lesion persisted a greater time in large lesions.

DISCUSSION OF RESULTS

This study represents more than 1,000 cases of vascular disease of the hemispheres. No attempt at a statistical analysis is made. Instead, emphasis is placed, as noted in the foregoing, on the use of dynamic electroencephalography and the resultant uniform picture produced. The picture in cerebral aneurysm and hemorrhage has been presented elsewhere.[3] In the case of thrombosis or embolus it is felt that there is always some associated vasospasm. This latter phenomenon may be minimal or may dominate the entire picture. Of the cases so studied, 90 per cent were thrombosis, embolus or vasospasm or a combination of the three. In addition, examples of associated cerebral edema with its resultant complicating clinical and electroencephalographic results are given. In some instances a combination of factors may be present.

For the most part, electroencephalograms were made with the Grass eight channel ink-writing electroencephalograph. At least 12 electrodes were applied, ten to the scalp and one to each ear. The scalp electrodes were placed in the usual frontal, parietal, occipital and anterior and posterior temporal sites. Recordings were taken, in most instances, with the scalp electrodes referred to both ears, the ipsilateral ear and to each other. Most electroencephalograms were taken using needle electrodes. Sleep records, spontaneous or induced, were obtained in some cases.

In all instances serial electroencephalograms were made. Each patient reported in this study had at least three electroencephalograms and some had as many as 15 to 20. Time of the electroencephalographic recording following the ictus varied from a few hours to three years. Special attempts at correlation of the clinical picture and progress with the electroencephalographic findings were always made. The clinical studies included, whenever possible, the following: history, physical and neurologic examinations, spinal fluid studies, pneumograms, arteriograms, operative reports, follow-up examinations and autopsy findings. In addition, comparisons were made with the electroencephalographic findings in neoplastic lesions, both benign and malignant.

The resultant picture in vascular lesions of the brain is a uniform one and can best be appreciated by a few general statements followed by several illustrative examples.

In lesions at or near the electroencephalographically accessible surface, the electrical picture is that of delta activity corresponding to the site of the lesion plus associated physiological alteration (e.g., vasospasm). This delta focus appears within a few hours at least following ictus. With a small lesion the electroencephalographic focus is small and sharp and may be limited to the vicinity of one or two electrodes. In a large lesion (e.g., thrombosis of an entire major vessel, such as the middle cerebral artery) the delta focus will be correspondingly greater. These foci may persist up to three to four months, depending on the extent of the lesion and the underlying pathology. In cases where there is much associated vasospasm the bulk of the focus will disappear within three to five days. In instances with appreciable edema there will be an increasing focus for three to ten days followed by a rapid resolution in the next three to five days. In all cases the electroencephalographic picture corresponds to the altering clinical picture and frequently heralds the clinical changes. In the few examples of infected emboli the electroencephalographic finding has been one of diffuse slowing plus the delta focus. Once the cerebritis has cleared the diffuse slow activity disappears.

In deep lesions of the brain, e.g., internal capsule and brain stem, there is usually very little, if any, delta activity in evidence. The only notable findings are the amplitude asymmetries.

The delta foci, when present, are usually discrete and well defined with

few exceptions. They may initially be obscured by the associated vasospasm and/or edema but by the seventh to tenth day they are sure to be prominent. In the case of expanding intracranial lesions the reverse is true. In these instances the foci not only become larger but the remote effects may become greater. In most cases the differential diagnosis of non-repetitive uncomplicated vascular lesions and neoplasms can be made within the first seven to ten days. In this period there is usually beginning resolution of delta activity in vascular disease.

PRESENTATION OF CASES

Case 1.— Focal cerebral vasospasm, right temporo-occipital region, associated with severe vascular headache.

G. N., a 22 year old right handed white woman, awakened at 11 a.m., on May 26, 1950 with a severe bifrontal and vertex headache. Thirty minutes later there was severe nausea and blurring of vision. Within one hour she became apprehensive and began to hyperventilate, during which time she noted tingling in the distal portions of her extremities and carpopedal spasm. At 3:30 p.m. she vomited and the headache, which was now generalized, became excrutiatingly severe.

The patient was examined six and one-half hours after the onset of headache and appeared acutely ill. Blood pressure was 136/90, temperature 98.0° F., pulse 88 and respirations 18 per minute. There was a left homonymous hemianopia and a mild left hemiparesis. Lumbar puncture revealed an initial pressure of 110 mm. of cerebrospinal fluid. There were no cells and the total protein was 33 mg. per cent.

By 9:30 p.m. the headache had markedly improved and the field defect had disappeared. The next day there was only a mild headache and the neurologic examination was entirely normal. Subsequently she remained asymptomatic. A combined pneumoencephalogram and right carotid arteriogram on May 31 was normal.

Electroencephalographic studies (figure 1): Initially, 24 hours after onset, there was a well defined delta focus in the right temporo-occipital area. Serial records showed rapid resolution of the delta activity, which was complete by the fifth day. The amplitude changes are of interest. Initially, from the first through the fifth days, the background activity or alpha voltage was decreased on the right side. By the nineteenth day the voltage on this side showed a tendency to increase, particularly in the posterior temporo-occipital region. Records taken 71 days and up to seven months following ictus, showed permanent ipsilateral voltage reduction.

Comment: Accelerated resolving delta activity is associated with rapidly altering clinical states. In this case, delta activity precipitated by the functional vascular changes of migraine cleared by the fifth day. The hasty disappearance of the clinical and electroencephalographic findings were probably due to focal cerebral vasospasm, possibly in asso-

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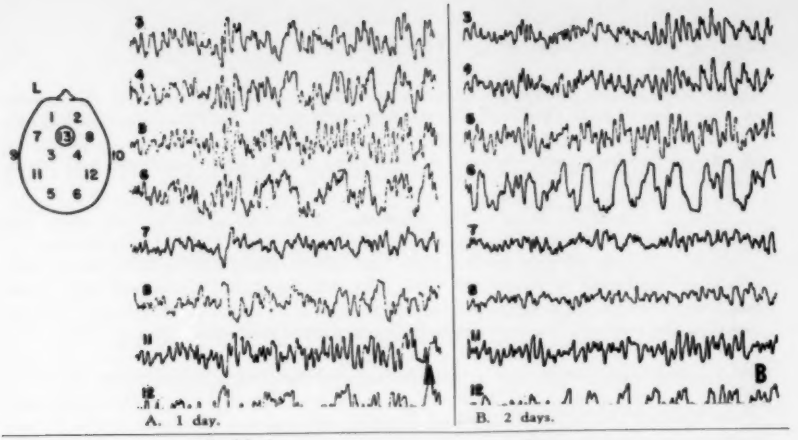
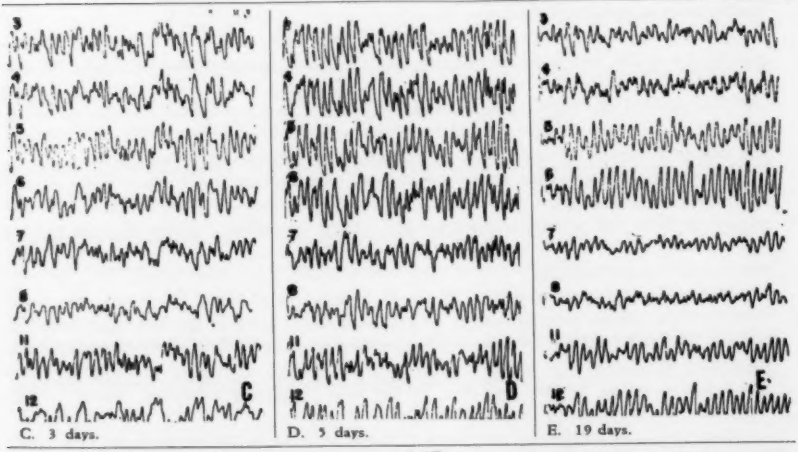
Fig. 1 (right). G. N. Focal cerebral vasospasm right temporo-occipital region associated with vascular headache. Left homonymous hemianopia and mild left hemiparesis on 5–26–50. Remission within 24 hours. Previous episode at age 18. Demonstrates: (1) Rapid resolution of delta focus within three days. This accelerated change is deemed compatible with functional (vasospastic) phenomena. (2) Serial changes in amplitude asymmetry after resolution of delta focus. In all vascular lesions the initial and permanent end result is ipsilateral amplitude reduction. However, at times, the EEG may show periods of increasing voltage lasting from 7 to 14 days.

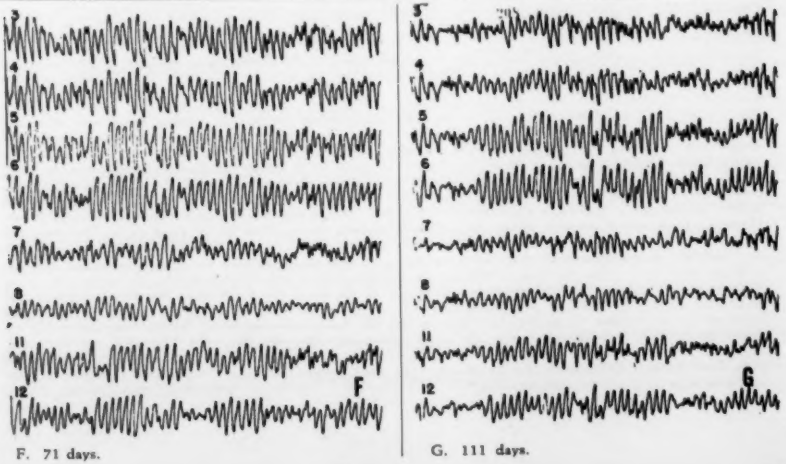
NOTE: A. Well defined delta focus in right temporo-occipital area, 24 hours after onset of headache. B. & C., Rapid resolution of focus within three days. A, B, C & D. Initial decreased amplitude of background activity ipsilateral to the lesion, best seen in the right temporo-occipital area. E. At 19 days the amplitude in the right temporo-occipital area is increased, best seen in electrodes 6 and 12. F & G. At 71 and 111 days the amplitude in the right anterior temporal region tends to be decreased and the increase in the occipital region is less marked. Subsequent records taken at 6 and 9 months showed moderate homolateral suppression.



A. 1 day. B. 2 days.



C. 3 days. D. 5 days. E. 19 days.



F. 71 days. G. 111 days.

Figure 1.

ciation with a small thrombotic lesion. A good prognosis was indicated by the presence of a well defined delta focus with minimal neurologic defect. Both the clinical and electroencephalographic changes resolved simultaneously. The serial alterations in amplitude are of interest and have been observed in all cortical lesions, e.g., thrombosis, hemorrhage, embolus, trauma, etc.

Case 2: Thrombotic lesion in the distribution of the left middle cerebral artery with associated cerebral vasospasm and meningeal reaction, presumably due to surface lesion.

O. B., a 29 year old right handed white man, experienced a sudden sensation of numbness in the right hand on January 29, 1945. This sensation spread up the arm to the shoulder, then down the right thigh and leg to the foot, after which it disappeared. He was seated at the time and the entire episode lasted about 15 minutes. He was aware of no weakness and had no disturbance of consciousness. Two hours later he became nauseated and vomited several times over a three hour period and had a mild bifrontal headache. He was then asymptomatic until the next morning when he awakened with a moderately severe bifrontal headache. Nausea and vomiting followed and shortly thereafter he was unable to speak coherently and was drowsy.

On examination at 9:00 a.m. on January 30, 1945, he had difficulty in using and interpreting the spoken word. Blood pressure was 150/80, temperature 98.4° F., pulse 54 and respirations 11 per minute. There was an incomplete right homonymous hemianopia, mild right hemiparesis and right extensor plantar response. Lumbar puncture revealed an initial pressure of 260 mm. of cerebrospinal fluid. There were 587 lyphocytes per cu. mm. and the total protein was 132 mg. per cent. Serologic tests for syphilis were negative.

By evening he became more alert and the dysphasia had improved. Speech was normal by the next day and memory for the events of the preceding day was complete. He remained afebrile and essentially asymptomatic. There remained a persistent right plantar extensor response. The spinal fluid on March 19, 1945 showed no cells and the total protein was 40 mg. per cent.

Electroencephalographic studies (figure 2): Initial record taken five hours after ictus showed slight diffuse slowing with a well defined delta focus in the left frontotemporal region. The delta activity rapidly resolved and disappeared within five days. Initially, up to five days, there was ipsilateral decrease in amplitude of background activity. This was followed by an increase and then by the final permanent reduction. These voltage alterations are best seen in the temporal and frontal areas.

Comment: The accelerated resolution of the delta focus in this instance associated with rapid clinical improvement is consistent with what one would expect in vasospastic phenomena. Residual right pyramidal signs indicate some degree of permanent damage. Cellular responses in the spinal fluid may be associated with thrombotic lesions of the cortical

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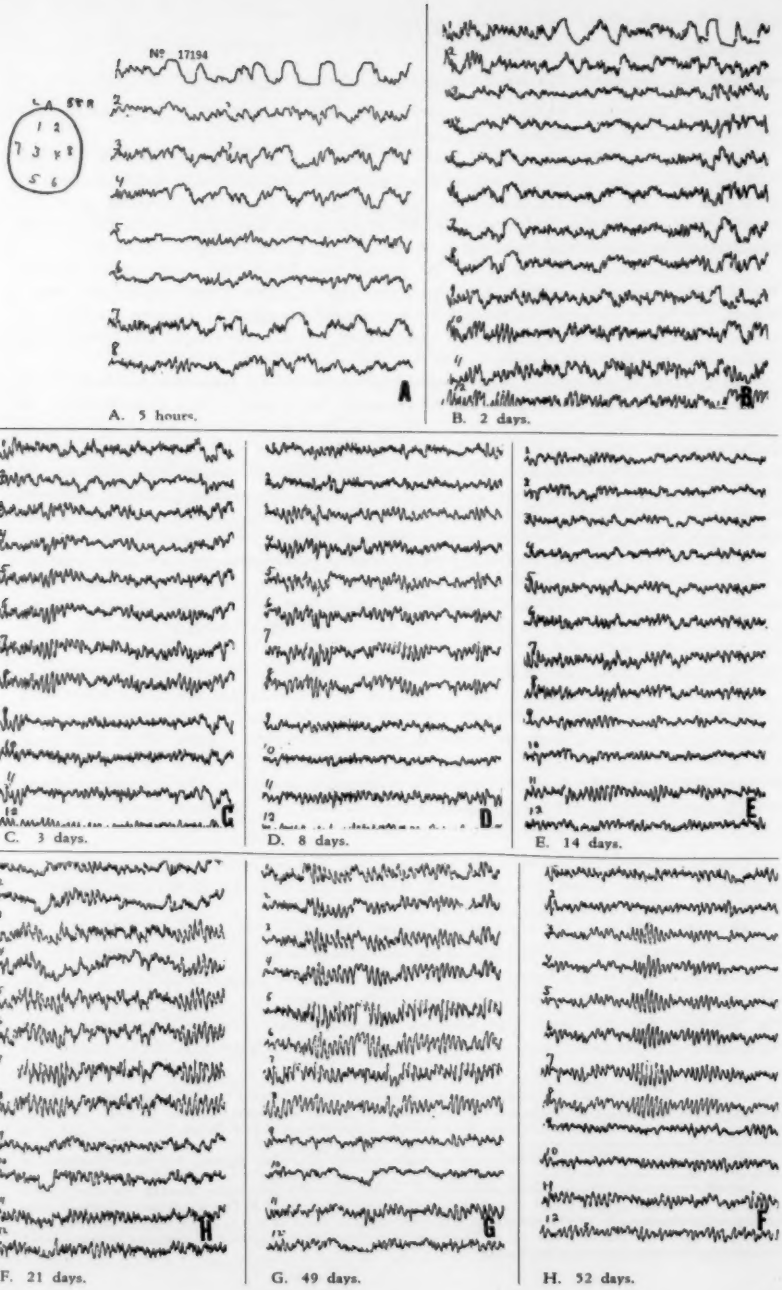
Fig. 2 (right). O. B. Thrombotic lesion in the distribution of the left middle cerebral artery with associated cerebral vasospasm. Focal right sensory seizure, 1–29–45. Semi-stupor, right hemiparesis, right homonymous hemianopia persisting for four hours on 1–30–45. Residual right pyramidal signs. Cellular reaction in spinal fluid. Demonstrates: (1) Rapid resolution of delta focus within 48 hours. This would be compatible with functional cerebral vascular changes. (2) Serial changes in amplitude asymmetry following resolution of delta activity. The initial change seems always to be ipsilateral amplitude reduction, which usually persists as long as the delta focus is present. This reduction is also the permanent end result. However, there may be several phases of amplitude increase lasting 7 to 14 or more days. The final picture is always that of ipsilateral depression, usually appearing no later than 6 months after ictus.

NOTE: A. Well defined delta focus in the left fronto-temporal area and mild generalized slowing, 5 hours after ictus. The background activity on the homolateral side is reduced in amplitude. B. & C. Resolution of delta activity within 48 hours. A, B, C, D, E, F, G & H show the serial alterations in amplitude. In the presence of focal delta activity (A & B) it is decreased (cf. electrode 1). This is then followed by an increase (C & D), best seen in the left fronto-temporal area. By the fourteenth day the amplitude is slightly decreased in the left anterior temporal electrode (E). On 21st (F) and 49th (G) days it is increased, but by the 52nd (H) day there is already shown the tendency to the final ipsilateral reduction. Records taken three and six months after ictus showed persistent 25 per cent reduction in voltage, best seen in the fronto-temporal region.



A. 5 hours.

B. 2 days.

C. 3 days.

D. 8 days.

E. 14 days.

F. 21 days.

G. 49 days.

H. 52 days.

Figure 2.

or ventricular surfaces.[8] The serial amplitude changes are again noted.

Case 3.—Thrombotic lesion in the distribution of the superficial branches of the left middle cerebral artery with meningeal reaction.

J. T., a 28 year old right handed white man, retired at midnight on January 22, 1948 with no evident illness and did not recover awareness until awakening in the hospital at 2:00 p.m. the next day. He vaguely recalled getting out of bed the preceding night but could not remember what had happened. There was a past history of four to five convulsive seizures in the previous three years.

On examination January 23, 1948 the patient was drowsy but responded to painful stimuli. Blood pressure was 124/70, temperature 99.6° F, pulse 60 and respirations 16 per minute. He had a moderate nuchal rigidity and a right hemiparesis. Lumbar puncture revealed an initial pressure of 70 mm. of cerebrospinal fluid. There were 120 lymphocytes per cu. mm. and the total protein was 46 mg. and sugar 56 mg. per cent.

On January 24 the level of consciousness had improved. He responded to all questions but had difficulty expressing himself. On January 26 dysphasia had improved but he complained of a severe frontal headache. Right hemiparesis persisted. On the evening of January 29, he had a generalized convulsive seizure. There were no alterations in his neurologic status following this. All physical abnormalities disappeared by February 10 except a persistent right extensor plantar response. The spinal fluid gradually improved so that by March 17 there were 37 lymphocytes per cu. mm. and the total protein was 38 mg. per cent. On June 15 there were no cells and the total protein was 13 mg. per cent.

Electroencephalographic studies (figure 3): Initial examination six days after ictus revealed moderate diffuse slowing with a delta focus in the left fronto-temporal region. On the eighth day (within 24 hours following a convulsive seizure) the diffuse slow activity had increased and masked the delta focus. As the generalized slowing waned the delta nidus was better defined (cf. 14 days and subsequently). At 11 months there was ipsilateral amplitude reduction, most marked in the left temporal and occipital electrodes.

Comment: Slow resolution of a delta focus as illustrated in this case is consistent with a relatively severe injury. Persistence of generalized delta activity for at least 14 days would indicate diffuse change as might be seen with cerebral edema, which may mask the delta focus. In a regressive lesion, clinical improvement may take place as long as delta activity is present. A favorable clinical prognosis is indicated in the presence of delta activity, particularly in view of the rapid neurologic recovery. Ipsilateral amplitude reduction represents the final end result and is permanent.

Case 4.—Thrombotic lesion in the distribution of the left middle cerebral artery associated with cerebral edema and with production of the picture of a focal expanding lesion. Episode possibly precipitated by seizures.

W. G. A., a 36 year old right handed white man, had a focal seizure on March 27, 1950, with twitching of the right side of the face and neck for five minutes without loss of consciousness. This was followed by severe left frontal headache and weakness of the right extremities for 30 minutes. He had several similar seizures on the same day and two on the following day, associated with momentary lapses of consciousness. Weakness of the right extremities persisted longer with each seizure and in the latter part of the second day

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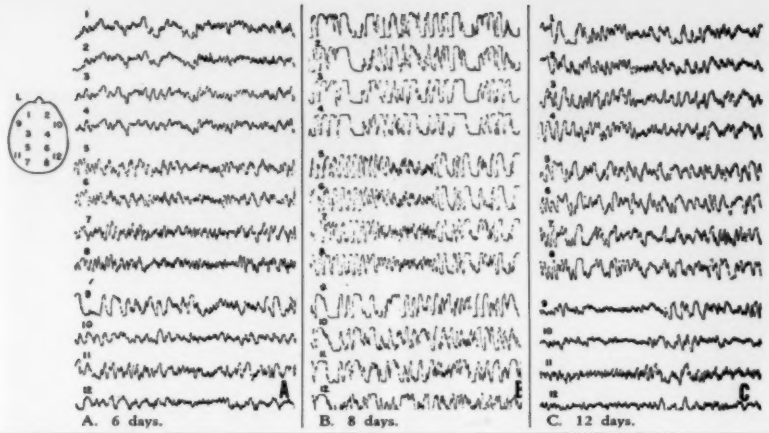
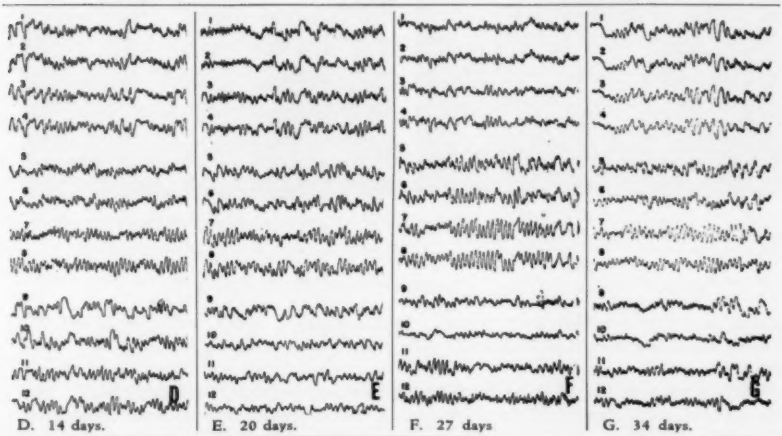
Fig. 3 (right). J. T. Thrombotic lesion in the distribution of the left middle cerebral artery with meningeal reaction. Right hemiparesis and drowsiness accompanied by signs of meningeal irritation on 1–23–48. Grand mal seizures on 1–29–48. Asymptomatic by 2–10–48. Demonstrates: (1) Initial delta focus and mild generalized slowing subsequent to ictus. (2) Increased generalized slowing after a seizure, followed by slow resolution, suggesting diffuse disturbance such as might be seen in cerebral edema. (3) Slow resolution of delta focus which would indicate a thrombotic lesion. (4) Final ipsilateral amplitude reduction.

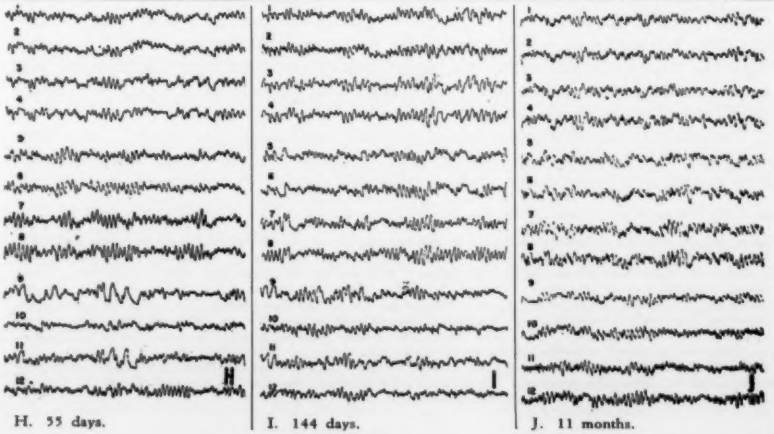
NOTE: A. Delta focus in left fronto-temporal region and mild generalized slowing, six days following ictus. B. Increased generalized abnormalities after seizure. A, B, C & D. Resolution of diffuse delta activity within 14 days. E, F, G & H. Slow resolution of delta focus in left temporal region, still not complete at 55 days. I. Ipsilateral increase in amplitude of background activity at 144 days and decrease at 11 months (J) following ictus (cf. electrodes 9 and 11).



A. 6 days. B. 8 days. C. 12 days.



D. 14 days. E. 20 days. F. 27 days G. 34 days.



H. 55 days. I. 144 days. J. 11 months.

Figure 3.

Fig. 4A. Ventriculogram eight days after onset of illness, showing filling defect in portion three of the left lateral ventricle.

Fig. 4B. Ventriculogram showing disappearance of defect 24 days later.

speech was impaired after each seizure. On March 29 difficulty with speech and left frontal headache persisted and became progressively more severe. On March 30 he became difficult to arouse.

On examination on March 31, 1950, the patient was lethargic. He had difficulty with the use and comprehension of the spoken word. Blood pressure was 130/80, temperature 98.6° F., pulse 80 and respirations 18 per minute. The right pupil measured 8 mm. and the left 6 mm. in diameter. Both responded sluggishly and through a poor range to flashlight. The left fundus showed blurring of the disc margins and engorgement of the veins. There was a marked right hemiparesis, right hemihypalgesia and right homonymous hemianopia. Lumbar puncture on April 1, revealed initial pressure of 310 mm. of cerebrospinal fluid. There were no cells and the total protein was 23 mg. per cent.

The patient's clinical status remained essentially unchanged until April 7, when lethargy began to clear rapidly. By April 17 there was definite improvement in the weakness of the right face and right lower extremity. The field defect had disappeared. He was able

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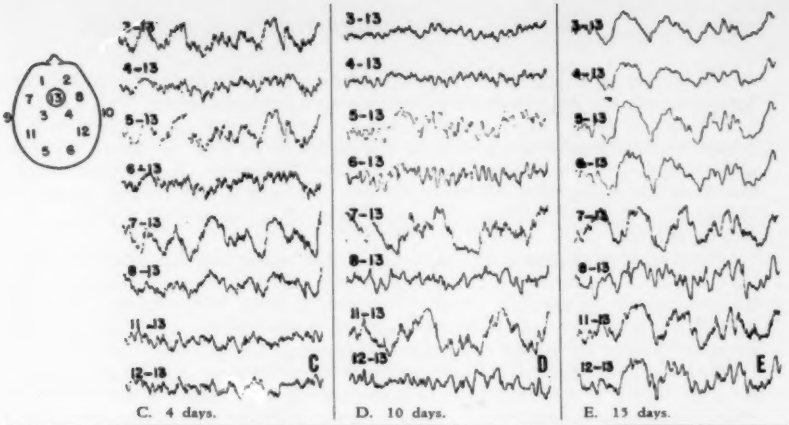
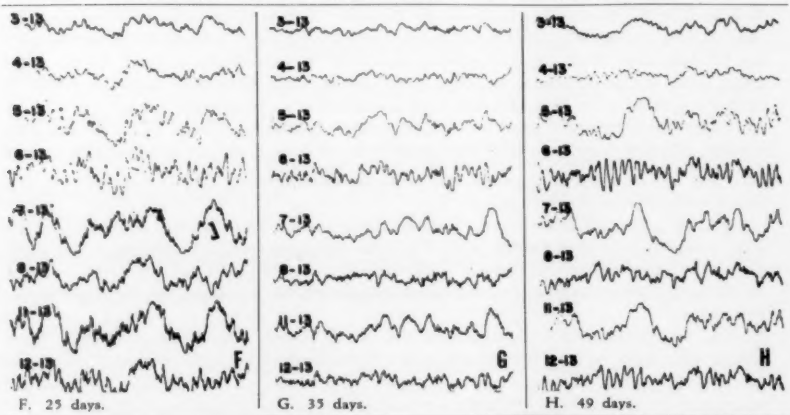
Fig. 4 (right). W.G.A. Thrombotic lesion in the distribution of the left middle cerebral artery with cerebral edema and production of syndrome of pseudotumor. Right sided focal seizures on 3–27–50 followed by increasing right hemiparesis, right sided sensory disturbances, dysphasia and right homonymous hemianopia. Decreased level of consciousness on 3–31–50. Condition stationary until 4–7–50 when lethargy cleared rapidly. Slow improvement in focal neurologic signs. Demonstrates: (1) Serial pneumographic studies of focal cerebral edema. (2) Increasing delta activity within first 15 days consistent with diffuse changes seen in cerebral edema. (3) Slow resolution of delta activity as seen in large thrombotic lesions. (4) Persistent ipsilateral reduction in background activity.

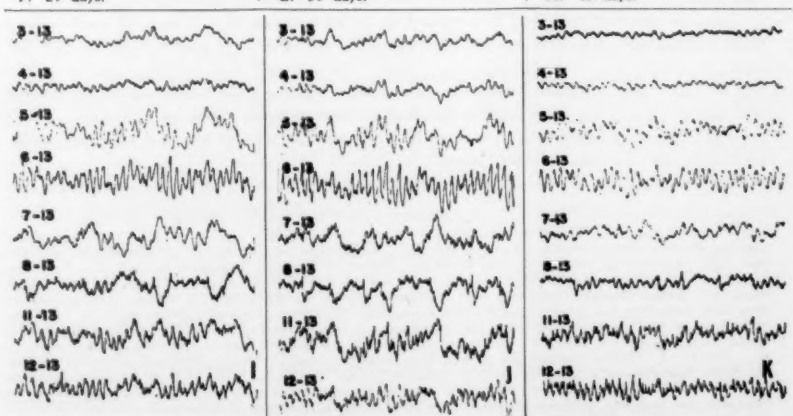
NOTE: C. Well defined delta focus in left temporal region, seen in initial EEG four days after onset. D & E. Increasing focal and diffuse delta activity within the first 15 days. F, G, H, I, J & K. Slow resolution of delta focus still not complete at 100 days.



C. 4 days. D. 10 days. E. 15 days.



F. 25 days. G. 35 days. H. 49 days.



I. 57 days. J. 71 days. K. 100 days.

Figure 4.

to walk by May 20. On July 5 he still had a moderate right hemiparesis more marked in the upper extremity and dysphasia more pronounced in the expressive sphere.

On April 4, 1950, a ventriculogram showed a definite though minimal shift from left to right with a filling defect in portion three of the left lateral ventricle. Repeat ventriculogram on April 28 showed moderate bilateral ventricular dilatation. The shift and defect in the ventricular system were no longer evident. Left carotid arteriography on May 11 showed narrowing of the left middle cerebral artery two and one-half centimeters from its point of origin.

Electroencephalographic studies (figure 4): Initial record four days after the onset of his illness revealed a marked delta focus in the left temporal region. At ten and 15 days the delta activity was increased, diffuse and masked the nidus. With resolution of the generalized slow waves the delta focus was again well defined (cf. 25 days). Complete resolution of the latter had not yet occurred at 100 days.

Comment: Subsequent to vascular lesions of the brain there may be progression of symptoms for one to three days followed by a relatively stable period of seven to 14 days before clinical improvement begins. Such changes may be due to cerebral edema and are indicated in the electroencephalogram by increasing diffuse delta activity. Pneumographic studies done during this initial period may show deformities of the ventricular system similar to those seen in an expanding lesion and lead to unnecessary surgery. In suspicious cases serial electroencephalograms will usually resolve the differential diagnostic difficulty within ten to fourteen days at which time changes due to edema will begin to resolve.

Long persistence of a delta focus in this instance indicates a large lesion involving the surface. Clinical improvement remains possible for at least as long as delta activity persists.

Case 5:—Thrombotic lesion in the posterior distribution of the left middle cerebral artery with mild cerebral edema.

J. L. A., a 30 year old right handed white man, awakened from sleep on April 19, 1950 with a severe pain over the left eye. The pain remained constant throughout the night. On the morning of April 20 there was paralysis of the right upper and moderate weakness of the right lower extremities. He also complained of numbness of the right upper extremity.

On examination, April 21, 1950, he was not in distress. Speech was normal. There was a right homonymous hemianopia and a right hemiparesis with marked weakness of the right lower face and right upper extremity. There was loss of vibratory, position and discriminatory sensations in the right extremities but no loss of pain sensibility.

Lumbar puncture on April 25 revealed an initial pressure of 170 mm. of cerebrospinal fluid. There were two lymphocytes per cu. mm., and the total protein was 17 mg. per cent.

By May 5 the right-sided weakness was minimal but the right homonymous hemianopia and loss of discriminatory sensation persisted. On examination July 10 and November 7, the right upper extremity was only slightly weak and the sensory loss was confined to this extremity. The hemianopia had cleared.

On May 1, 1950, a pneumoencephalogram showed a slight shift of the ventricular sys-

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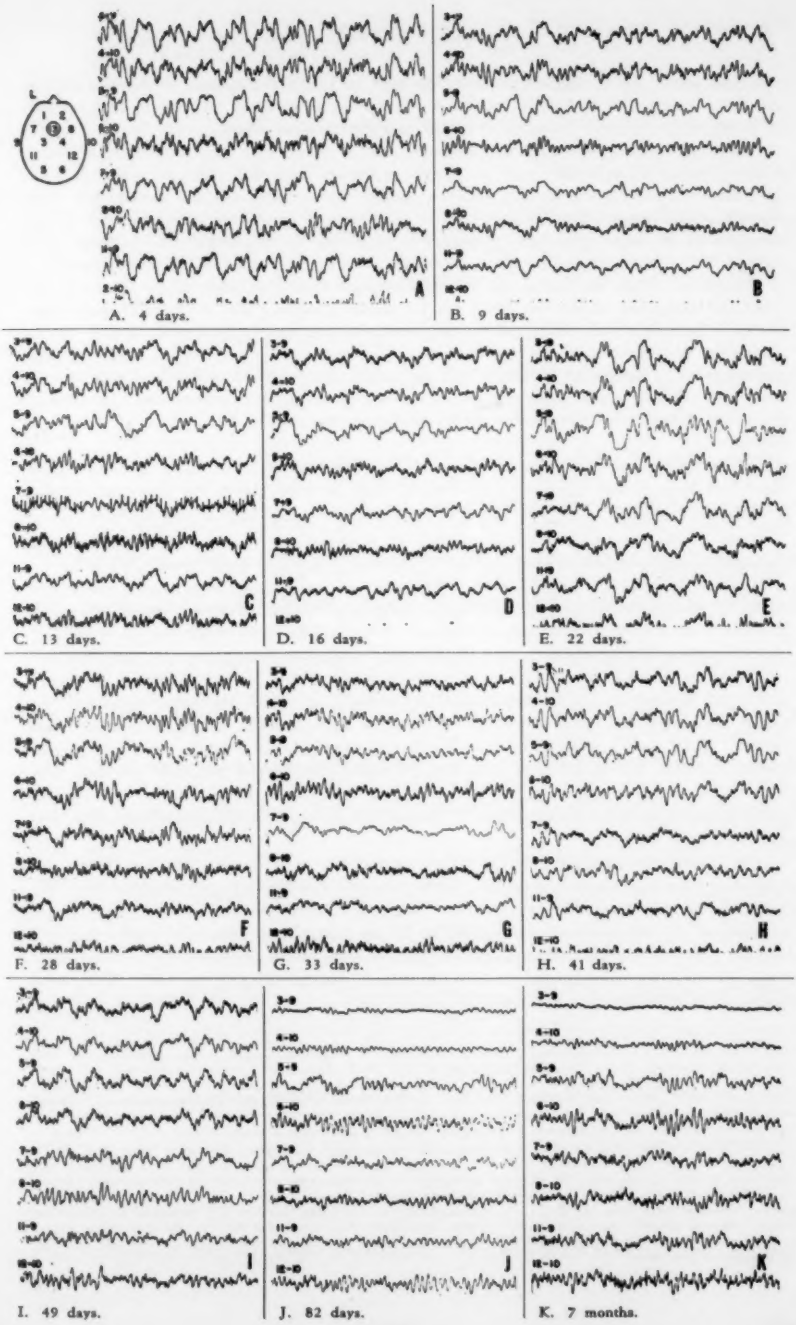
Fig. 5 (right). J. L. A. Thrombotic lesion in the posterior distribution of the left middle cerebral artery with associated cerebral edema. Right hemiparesis, right sided impairment of discriminatory sensation and right homonymous hemianopia on 4–19–50. Weakness markedly improved by 5–3–50. Persistent slight weakness and sensory disturbance on 7–10–50 and 11–7–50. Demonstrates: (1) Marked initial delta focus and diffuse slowing, compatible with a cortical lesion. (2) Resolution of diffuse delta activity by nine days, indicating (a) a regressive disorder permitting exclusion of neoplastic disease and (b) rapid improvement such as seen in vasospasm and/or edema. (3) Slow resolution of delta focus suggestive of severe local injury. (4) Persistent decreased amplitude in background activity ipsilateral to the lesion.

NOTE: A. Diffuse slowing and marked delta focus best seen in the left temporal and occipital areas. B. Rapid resolution of diffuse delta activity within nine days. C, D, E, F, G, H, I & J. Slow resolution of delta focus, still not complete at 82 days. Ipsilateral reduction in amplitude of background activity is persistent and best seen in the temporal and occipital areas. K. Absence of delta focus and ipsilateral amplitude reduction seven months after ictus.



A. 4 days.

B. 9 days.

C. 13 days.

D. 16 days.

E. 22 days.

F. 28 days.

G. 33 days.

H. 41 days.

I. 49 days.

J. 82 days.

K. 7 months.

Figure 5.

tem from left to right. Repeat air study on May 16 revealed a normal ventricular system and the previous shift had disappeared. A left carotid arteriogram on May 16 showed lack of filling of the posterior branches of the left middle cerebral artery.

Electroencephalographic studies (figure 5): Initial record four days after onset of illness revealed diffuse slow activity with a delta focus marked over the entire left side. By nine days the slow activity was already resolving and the delta focus was less marked but more discrete. Subsequent records showed serial resolution of delta activity which was almost complete by 82 days. Ipsilateral reduction of amplitude of the background activity, most marked in the temporal and occipital areas, was constant and still seen at seven months.

Comment: With the initial electroencephalogram four days after onset of symptoms, a definite diagnostic impression could not be made. Coupling this record with one taken five days later, however, confirmed the impression of a regressive (vascular) lesion. Pneumographic studies were suggestive of a space occupying lesion or edema, and a repeat pneumogram 15 days later indicated that the initial changes were probably due to thrombosis and edema, which confirmed the electroencephalographic impressions. An arteriogram was suggestive of occlusion of the posterior branches of the left middle cerebral artery.

Little further clinical improvement could be expected after 82 days, at which time there had been almost complete resolution of delta activity. Once the slow activity has resolved little anatomico-clinical recovery can be expected.

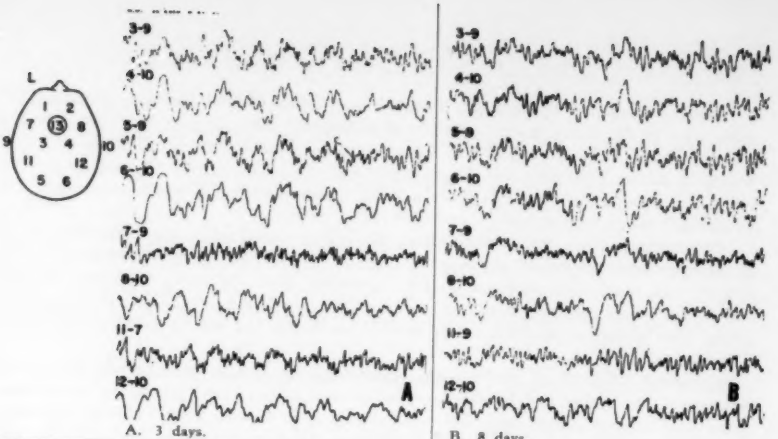
Case 6.—Meningovascular neurosyphilis with a thrombotic lesion in the distribution of the right middle cerebral artery.

L. G., a 51 year old right handed colored woman, was in good health until May 1949. At that time she began to have throbbing suboccipital and retro-orbital headaches which progressed until they were almost continuous. Early in July 1949 there was an episode of unconsciousness lasting approximately 15 minutes. Upon awakening she was confused and unable to use the left extremities. Confusion disappeared but she remained slightly weak in the left extremities. Subsequently she had episodes in which she acted peculiarly, sat staring into space and fumbled with her clothing or walked about the house in a confused fashion. Blood and cerebrospinal fluid serological reactions for syphilis were positive on August 2, 1949. The spinal fluid contained 2 lymphocytes per cu. mm. and the total protein was 80 mg. per cent. On August 14 she had a "mild shaking spell," complained of a severe headache and became lethargic. Drowsiness increased until admission to the hospital on August 16.

On examination August 16, 1949, the patient was very drowsy but would respond sluggishly when her name was called. Blood pressure was 208/100, temperature 99.8° F., pulse 86 and respirations 16 per minute. There was a left homonymous hemianopia and weakness of the left extremities estimated at 50 per cent. There was mild nuchal rigidity. Lumbar puncture revealed an initial pressure of 265 mm. of cerebrospinal fluid. There were 6 lymphocytes per cu. mm. and the total protein measured 121 mg. per cent. Blood and cerebrospinal fluid Kahn reactions were positive in high titer.

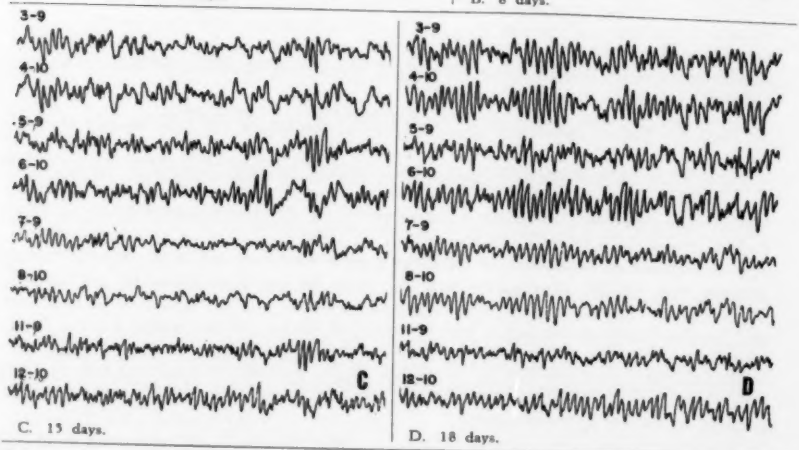
Fig. 6 (right). L. G. Meningovascular neurosyphilis with a thrombotic lesion in the distribution of the right middle cerebral artery. Recurrent headaches in May 1949. Episodes of confusion and mild left hemiparesis in July 1949. Marked left hemiparesis and left homonymous hemianopia on 8–14–49. Rapid clinical improvement while under penicillin therapy. Asymptomatic by 9–15–49. Demonstrates: (1) Initial marked delta focus denoting site of cortical lesion. (2) Rapid resolution of delta activity associated with clinical improvement. (3) Alterations in amplitude following resolution of delta focus.

NOTE: A. Marked delta focus over entire right side in EEG taken three days after ictus. B, C & D. Resolution of delta focus within 18 days. A, B & C. Initially the background activity is decreased (cf. electrodes 8–10). C. By the 15th day the amplitude in the right posterior temporal and occipital regions is tending to increase, concomitant with the disappearance of the delta focus. This change is pronounced by the 18th and 24th days (D & E). F. Although on the 32nd day there is still ipsilateral amplitude increase, there is already seen a tendency towards depression, (cf. electrodes 8–10). Records taken subsequently showed persistent homolateral decrease in amplitude. Frequently the amplitude changes may lag or precede in one area.



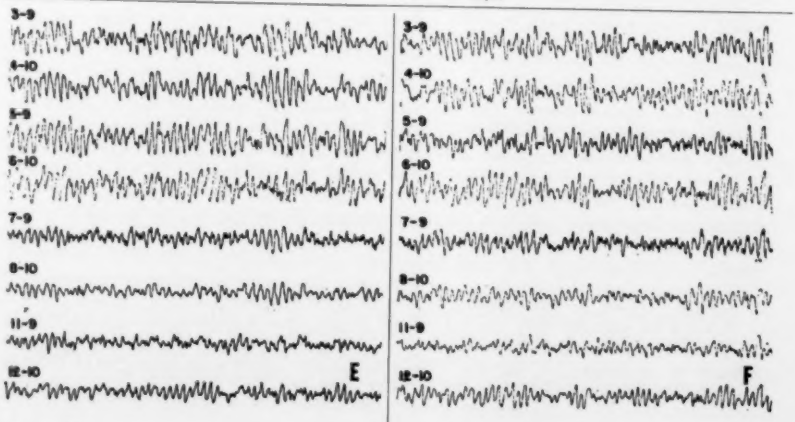
A. 3 days.

B. 8 days.



C. 15 days.

D. 18 days.



E. 24 days.

F. 32 days.

Figure 6.

Procaine penicillin therapy was initiated on August 17 and she was given 300,000 units every twelve hours to a total dosage of 12,000,000 units. Sixteen hours after the first dose of penicillin there was a rise in temperature to 101.4° F. which fell again to normal within 24 hours. Following this, improvement was rapid. By August 22 she was ambulatory. The hemiparesis cleared rapidly and by September 15 she was asymptomatic but an incomplete left homonymous visual field defect persisted.

Electroencephalographic studies (figure 6): Initial record taken three days after onset of lethargy shows delta activity marked over the entire right side. Resolution of delta activity was rapid and complete by the eighteenth day. Following resolution of delta activity there was ipsilateral amplitude increase, best seen in the right temporal and occipital areas. This tended to decrease on the twenty-fourth day but was again increased on the thirty-second day.

Comment: Activity of the syphilitic process in this case is presumed by the febrile response to treatment[9] and by the presence of cells and elevated protein in the cerebrospinal fluid. Rapid clinical and electroencephalographic improvement following institution of penicillin therapy would indicate a rapidly reversible process such as might be seen with functional (vasospastic) vascular change and with a focal syphilitic encephalopathy. The presence of delta activity initially indicated that improvement in the neurologic defect was possible and that the lesion involved the surface. Subsequent electroencephalograms showed ipsilateral amplitude decrease.

Case 7.— Surface thrombotic lesion in the distribution of the right middle cerebral artery, initially mistaken for a capsular thrombotic lesion.

M. S. W., a 51 year old right handed white woman, suddenly slumped to the floor and was unable to move the left extremities. There was no loss of consciousness. In the following 13 days there was no improvement in the paralysis. She remained relatively comfortable except for mild right sided headaches.

On examination September 4, 1950, the patient was alert and in no distress. Blood pressure was 100/60, temperature 98.6° F., pulse 82 and respirations 14 per minute. There was a complete left hemiplegia, left hemihypalgesia and left homonymous hemianopia. Lumbar puncture revealed an initial pressure of 150 mm. of cerebrospinal fluid. There were 2 lymphocytes per cu. mm. and the total protein was 20 mg. per cent.

Improvement was slow but by November 29 she was able to walk and had an estimated weakness of 60 per cent in the left lower extremity and almost complete spastic paralysis of the left upper extremity.

Electroencephalographic studies (figure 7): Initial record 15 days following ictus revealed a marked delta focus over the entire right side, maximal in the frontal and temporal areas. On the ninety-ninth day the delta focus was still marked but less so than previously.

Comment: Initially, from the clinical standpoint, it was felt that the lesion was deep, involving the internal capsule. On this basis prognosis for significant functional recovery was thought to be poor. However, the marked delta focus seen in the electroencephalogram 15 days after ictus was interpreted as being due to the presence of a large superficial lesion such as might be caused by occlusion of the middle cerebral artery, and hence, indicated a more guarded and favorable prognosis. That a delta focus was still present at 99 days indicated a large lesion and that complete anatomic repair had not as yet taken place. Further clinical recovery could be expected. Improvement continued until the fourth month.

Case 8.—Thrombotic lesion involving the left internal capsule.

L. G., a 51 year old right handed colored woman, had a sudden onset of inability to move the right extremities at 11:00 p.m. on January 15, 1951. Following this there was difficulty in swallowing, in that she choked easily and liquids were regurgitated through the nose. Speech was a whisper and was nasal in quality.

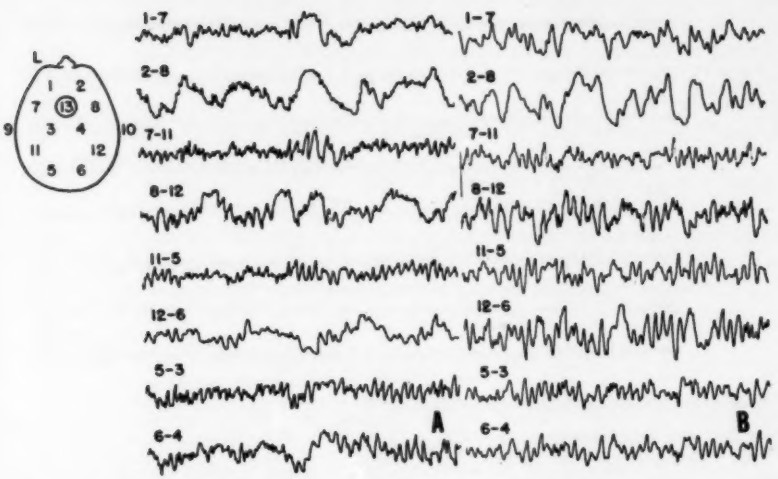


Fig. 7. M. S. W. Thrombotic lesion in the distribution of the right middle cerebral artery. Sudden onset of left hemiplegia, left homonymous hemianopia and left hemihypalgesia on 8–22–50. Slow improvement in the neurologic defect. Walking by 11–29–50. Left homonymous hemianopia and left sensory defect disappeared. Demonstrates: (1) Prognostic and localizing value of the electroencephalogram. When the patient was seen initially it was felt that the lesion was in the internal capsule and hence offered a poor prognosis from the standpoint of recovery. However, after an EEG was obtained, it was felt, in view of the pronounced delta focus, that the lesion was closer to the surface and offered a better clinical prognosis. (2) Slow resolution of delta activity.

NOTE: A. Marked delta focus over entire right side, maximal in the fronto-temporal area, 15 days after ictus. B. Delta focus still marked but less severe at 99 days.

Previously in 1937 the patient had had a left hemiparesis of sudden onset followed by mild residual weakness of the left extremities. There had been repeated episodes of congestive heart failure due to hypertension since 1945.

On examination January 16, 1951, the patient was alert but uncomfortable because of dyspnea. Blood pressure was 210/110, temperature 98.0° F., pulse 80 and respiration 18 per minute. There was marked dysarthria and dysphagia and a complete right hemiplegia. Snout and sucking reflexes were present and there were bilateral extensor plantar responses. Lumbar puncture revealed an initial pressure of 125 mm. of cerebrospinal fluid. There were no cells and the total protein was 26 mg. per cent.

By February 28 there had been no significant improvement in the neurologic status of the patient. The complete right hemiplegia persisted.

Electroencephalographic studies (figure 8): Initial record nine days following ictus revealed a reduction in amplitude on the left side most marked in the temporo-occipital area. Ipsilateral amplitude reduction was still present at 15 and 18 days. No delta activity was observed.

Comment: This patient presented the symptoms and signs of a severe neurologic defect with a pseudobulbar palsy and right hemiplegia. The lesion responsible for the more recent ictus was clinically localized to the left internal capsule, hence prognosis for significant functional recovery would be poor. Absence of delta activity is seen with deep lesions not involving the surface and further indicates a poor prognosis.

Initial and final ipsilateral amplitude reduction of alpha or background activity may be the sole electroencephalographic lateralizing sign in deep lesions.

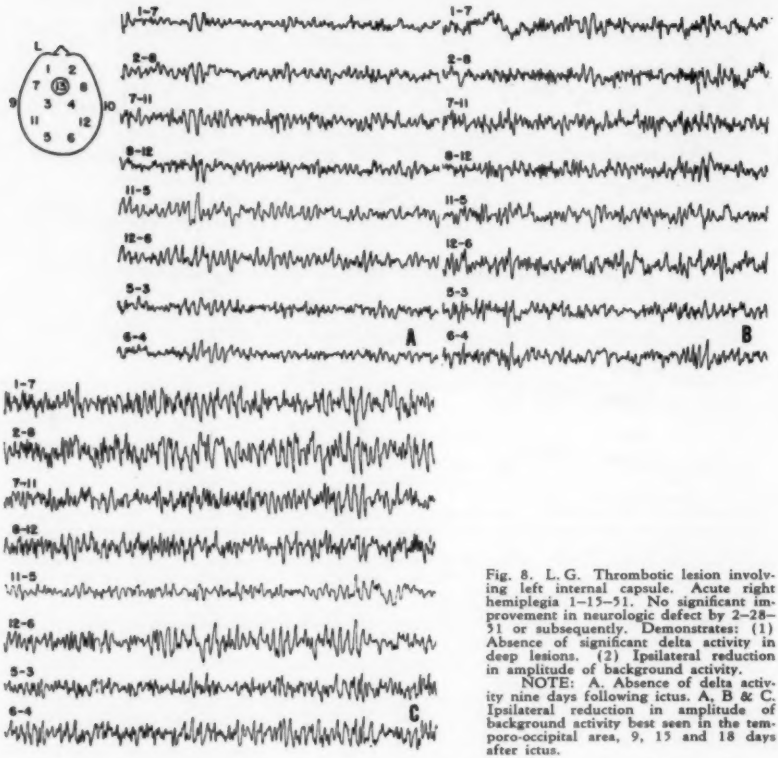


Fig. 8. L. G. Thrombotic lesion involving left internal capsule. Acute right hemiplegia 1–15–51. No significant improvement in neurologic defect by 2–28–51 or subsequently. Demonstrates: (1) Absence of significant delta activity in deep lesions. (2) Ipsilateral reduction in amplitude of background activity.

NOTE: A. Absence of delta activity nine days following ictus. A, B & C. Ipsilateral reduction in amplitude of background activity best seen in the temporo-occipital area, 9, 15 and 18 days after ictus.

SUMMARY AND CONCLUSIONS

The dynamic use of the electroencephalograph in the study of cerebral vascular lesions is presented. Emphasis is placed upon serial correlated studies as an aid in localization, differential diagnosis and prognosis. Statistical analysis is not presented.

The initial changes after a vascular insult to the brain depend upon the localization of the lesion and upon associated phenomena such as vasospasm and edema. With a superficial lesion delta activity is prominent, but minimal or absent in deep subcortical lesions. Rapid resolution (two to five days) is seen in cerebral vasospasm. In cerebral edema secondary to a thrombotic lesion there may be increasing delta activity which usually begins to resolve within ten to 14 days. Resolution of delta activity in a regressive lesion such as thrombosis or embolus is usually complete by the third month but varies with the size and severity of the lesion.

Serial changes in amplitude asymmetry occur but are usually stable by the sixth month. Initially in the first week, with or without a delta focus, there is almost universal voltage reduction ipsilateral to the lesion. This may be replaced by one or more phases of increased amplitude each usually lasting seven to 14 or more days. Increased voltage usually does not appear until after resolution of slow activity. Permanent ipsilateral voltage reduction is usually present by the sixth month.

In a regressive lesion, the presence of delta activity indicates that further organic improvement is possible, hence a guarded prognosis. Absence of delta activity in the presence of neurologic defect indicates either a deep lesion (such as brain stem or internal capsule) or that maximal recovery has occurred, hence indicates poor prognosis for further functional recovery.

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The *attack* of congestion, or of haemorrhagy itself, is frequently of the most sudden kind. There are total loss of sense and motion; the patient is flushed, comatose, breathes with stertor, and the pulse is strong and full. This is probably the case of congestion. In the attack of considerable hemorrhagy, there are the symptoms of *shock* inflicted upon the nervous system: pain of the head is followed by paleness, sickness and vomiting, and fainting; coma, or paralysis, loss of speech, or of the power of swallowing, succeed immediately or more slowly, probably according to the promptitude or the extent of the haemorrhagy. In the attack of partial haemorrhagy, these symptoms are observed in a slighter form; and it is some paralysis, hemiplegia, partial loss of speech, &c. which ensues. In one interesting case, such an attack as I have last described was followed in a few months by one of severer form, and the patient survived but a few days.

Marshall Hall in *Lectures on the Nervous System and its Diseases,* published in 1876.

Metabolic Disorders in Paraplegics

Irving S. Cooper, M.D. and Thomas I. Hoen, M.D.

It is the purpose of this report to summarize briefly observations concerned with metabolic abnormalities observed in paraplegic patients. This review included clinical data on over 300 paraplegic patients studied during the past five years. The majority of these were paraplegic as a result of traumatic lesions of the spinal cord, and, except where otherwise indicated, this discussion deals specifically with traumatic paraplegics.

PROTEIN METABOLISM FOLLOWING SPINAL CORD INJURY

Any acute injury to the spinal cord which is severe enough to cause paraplegia or quadriplegia produces a marked catabolism of body protein. This is reflected in the urinary excretion of large amounts of nitrogen. Up to 30 grams of nitrogen, representing 186 grams of protein, may be excreted daily for two to four weeks. During the first two weeks after injury there is invariably a markedly negative nitrogen balance which may amount to as much as 25 grams of nitrogen per day. Moreover, the administration of a high protein diet does not mitigate the negative nitrogen balance, but rather increases nitrogen output. This latter finding is in accord with previous reports concerning the protein metabolic response to trauma,[1,2] and accounts for the commonly encountered clinical difficulties in maintaining an adequate nutritional status in paraplegics. In the majority of cases, a normal nitrogen balance is re-established eight to ten weeks after injury. However, in many instances a negative nitrogen balance has been observed to persist as long as 14 months after the original injury.

The source of nitrogen appearing in the urine is the general body store of protein, particularly muscular tissue. The distribution of nitrogen in the urine is essentially the same as that in the urine of healthy adults, that is, approximately 80 per cent of the urinary nitrogen is excreted in the form of urea.

From the department of neurosurgery, New York University-Bellevue Medical Center, New York City.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1951.

This survey includes patients examined in the paraplegic center, U. S. Naval Hospital, St. Albans, Long Island, New York; Mayo Clinic, Rochester, Minnesota; and the New York University-Bellevue Medical Center.

However, the amount of nitrogen excreted as creatine is disproportionately increased, and marked creatinuria is observed during the first six to ten weeks after spinal cord injury. The urinary excretion of creatine may reach levels as high as 110 mgm. in 24 hours.

The severity of the catabolic reaction, as reflected in the urinary excretion of large amounts of nitrogen and marked creatinuria, appears to be directly proportional to the severity of spinal cord injury. It has been noted that the excretion of more than 25 grams of nitrogen in the urine per 24 hours during the first two weeks after injury usually indicates a poor prognosis as regards eventual return of function of the paralyzed muscles. This parallels the observation of MacCarty that a severe catabolic reaction following intracranial injuries, as reflected in a marked persistent azotemia, bespeaks a poor prognosis.[3] In severely injured patients there is often a precipitous fall in the level of serum proteins with a tendency towards reversal of the albumin-globulin ratio. The serum proteins may reach levels as low as 4.6 grams per 100 cc. within 14 days after injury.

The protein catabolic response to trauma is most vigorous in normal healthy young male adults, who constitute the majority of cases of traumatic paraplegia. Previously debilitated patients do not exhibit a marked creatinuria or elevated urinary nitrogen excretion in response to trauma or disease.[4] However, several patients in this series over the age of 65 years have been observed to respond to spinal cord injury with an intense catabolic reaction. Spinal cord injuries resulting in quadriplegia appear to result in a quantitatively greater catabolic reaction than those producing paraplegia; this suggests that the degree of protein breakdown may be partially determined by the amount of muscular tissue which is paralyzed. Although the mechanism responsible for the catabolic reaction has not yet been satisfactorily elucidated, Howard[2] has summarized succinctly the known facts about post-traumatic catabolism of body protein as follows: Nitrogen loss is produced by the increased urinary excretion of nitrogen, the fecal excretion of nitrogen being no greater than a normal amount of nitrogen in the stools. The disposition of the nitrogeneous portion of catabolized protein after trauma follows the same pattern as in health, urea constituting about 80 per cent of the total urinary nitrogen. Fever alone will not produce the reaction. Atrophy of disuse and bed rest will account for only a small part of the nitrogen loss. High caloric diets with large quantities of protein often do not appreciably spare the body nitrogen at the height of a vigorous protein catabolic reaction, whether the protein is administered orally or intravenously.

LIVER FUNCTION FOLLOWING SPINAL CORD INJURY

Impaired liver function, as evidenced by the bromsulfalein liver function test, has been observed in many cases of severe acute spinal cord injury.[5] No other commonly employed liver function tests have demonstrated abnormality in these cases. The average degree of bromsulfalein retention which

has been observed in acute paraplegics was 27.7 per cent within 60 minutes after administration of the dye. This impairment of liver function resolves spontaneously within eight to ten weeks after injury, and is not demonstrable in chronic paraplegics. However, approximately 20 per cent of chronic paraplegics demonstrate some degree of hepatomegaly, and amyloidosis of the liver has been reported to occur in paraplegics.[6,7]

The mechanism of impairment of liver function in acute paraplegics is not clear. Whether this phenomenon is related to a similar, although quantitatively less marked, impairment of liver function observed by Beecher[8] in severely wounded soldiers cannot yet be stated. It is interesting to note in this regard that Selye has reported physiologic and morphologic changes in the liver during the alarm reaction.[9,10] The fact that during spinal shock there is vasodilatation of all blood vessels below the level of spinal cord injury suggests the possibility that circulatory stasis in the abdomen during the period of spinal shock may play some part in this dye retention in acute paraplegics.[11]

BASAL METABOLIC RATE IN PARAPLEGICS

The basal metabolic rate is almost invariably decreased in paraplegics, and values as low as minus 24 per cent have been recorded in patients in whom there was no other evidence of hypothyroidism. Protein-bound iodine determinations and blood cholesterol values in such cases have been within normal limits. Although the physiologic basis for a decreased metabolism in paraplegics is not yet established, several previous reports are pertinent to this subject. Traumatic shock,[12] burns[13] and other types of stress[9] have been reported to result in an early decrease in the basal metabolic rate. The immobilization of paralyzed extremities may contribute to a lowered oxygen consumption in such patients.

GYNECOMASTIA IN PARAPLEGIC MALES

Unilateral or bilateral mammary enlargement develops in approximately 20 per cent of men who are paraplegic as a result of a traumatic spinal cord lesion. It may appear as early as three months after incurrence of the lesion[14] or as late as five years after injury. The enlarged breasts are painful and tender in 50 per cent of those who develop them. The breast enlargement usually disappears within three months of the time of its appearance, but has been observed to persist as long as 12 months. Testosterone therapy will relieve the pain associated with this type of gynecomastia, and may result in rapid resolution of the breast hypertrophy. Typical examples of gynecomastia in paraplegic males are pictured in figure 1.

The pathogenesis of gynecomastia in paraplegic males is not yet clear. It is conceivable that malnutrition and impaired liver function may play a role in producing breast enlargement, as has been reported to occur in malnourished prisoners of war.[15,16] Testicular atrophy may be instrumental in the development of mammary enlargement in these men[17] or, as suggested

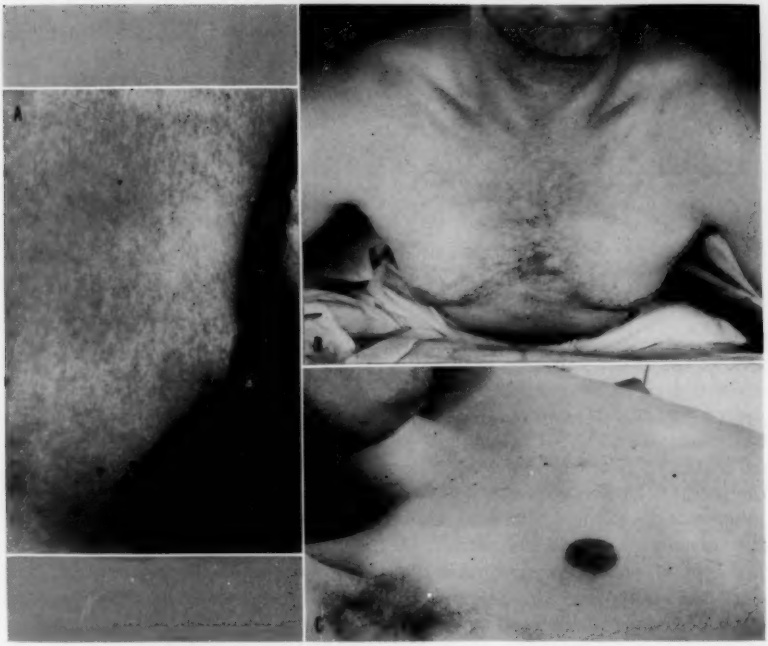

FIG. 1. Gynecomastia in paraplegic males. a) Breast enlargement in 16 year old boy beginning three months after spinal cord injury. b) Gynecomastia in 40 year old paraplegic two years after injury. c) Mammary enlargement in 22 year old paraplegic eleven months after injury. Note enlargement of nipples.

previously, the metabolic effects of the alarm reaction may play some role in the pathogenesis of gynecomastia following spinal cord injury.[18]

TESTICULAR ATROPHY IN PARAPLEGIC MALES

Testicular atrophy occurs in over 50 per cent of paraplegic males. This is occasionally observable grossly,[19] but usually requires biopsy confirmation.[20,21] Microscopic examination usually reveals marked atrophy of the germinal epithelium of the seminiferous tubules with aspermatogenesis; occasionally there is hyperplasia of the interstitial elements (figure 2). Neurogenic hypogonadism has also been reported to occur in cases of Friedreich's ataxia,[22–25] diabetic genitourinary neuropathy[26] and syringomyelia.[19] Sexual potency and fertility in paraplegic men has been discussed by Munro, Horne and Paull[27] and Bors and associates.[28] Bustamente has suggested that a descending nervous pathway from the hypothalamus to the gonads via the spinal cord is essential for the proper maturation of the germinal epithelium.[29] Moreover, it has recently been reported that descending spinal pathway from the hypothalamus to the

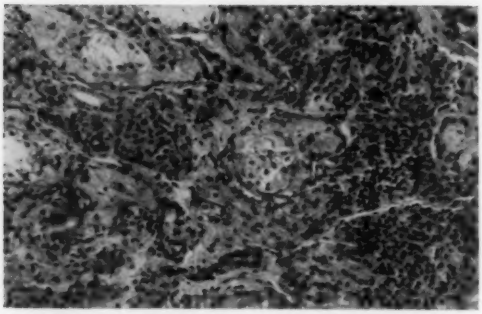

FIG. 2. Microscopic section of testicular biopsy demonstrating atrophy of germinal epithelium of seminiferous tubules. There is marked hyperplasia of interstitial elements.

ovaries may be essential to maturation of ova and ovulation.[30] Therefore, one must consider the possibility that descending hypothalamic-spinal pathways are essential to the reproductive functions of the gonads in both sexes.

HORMONE EXCRETION IN PARAPLEGIC MALES

During the first 48 hours following a severe spinal cord injury there is a temporary elevation of the 17-ketosteroids appearing in the urine. Following this period, the urinary excretion of the 17-ketosteroids is decreased in 50 per cent of paraplegic men, lasting from ten weeks to several years. There has been a complete disappearance of 17-ketosteroids from the urine in several cases. In approximately 10 per cent of cases the urinary excretion of cortin-like substances is also decreased. Bors et al[28] have reported abnormally elevated urinary titers of the 17-ketosteroids in some paraplegic males.

In three paraplegic men who demonstrated gynecomastia pathologically, elevated urinary titers of follicle stimulating hormone have been observed.[18] However, in most instances the urinary excretion of this hormone has been reduced. It has not been possible to demonstrate increased urinary excretion of estrogens in any of the cases in whom the urine has been examined for estrogenic substances, including those paraplegics who demonstrated gynecomastia.

MENSTRUAL DISORDERS IN PARAPLEGIC FEMALES

Following a severe spinal cord injury in young adult females there is a cessation of menstruation for a period of three to six months. In most instances there is a resumption of menstruation after this period, but the menses are much scantier than they had been previously and often occur at irregular intervals. A detailed investigation of the metabolic consequences of spinal cord trauma in females is currently in progress.

EOSINOPENIC RESPONSE TO SPINAL CORD TRAUMA

It has been possible to obtain absolute circulating eosinophil counts in six men within 24 hours after severe cord injury. In all six cases, eosinophils

were absent from the peripheral blood. In four of these the circulating eosinophil count returned to normal levels within 48 hours, while in the remaining two patients the normal level of circulating eosinophils was not encountered until four days after the injury had been incurred. This striking eosinopenic response to spinal cord trauma is believed to be a reflection of the alarm reaction stimulated by spinal cord trauma. It has been reported previously that spinal cord transection is a particularly potent alarming stimulus in the rat.[31] Moreover, spontaneous gastrointestinal hemorrhages have been observed to occur in three cases of cervical cord injury. Selye has pointed out that acute gastrointestinal erosions are common sequelae of a vigorous alarm reaction.[10]

TESTOSTERONE AS AN ANTICATABOLIC AGENT IN PARAPLEGICS

Because of the metabolic abnormalities occurring in paraplegic men, particularly gynecomastia, testicular atrophy and decreased excretion of the 17-ketosteroids, it seemed probable that testosterone therapy might be of some value in the medical adjunctive therapy of paraplegics. Moreover, in view of the altered protein metabolism in these patients, and the difficulty encountered clinically in maintaining an adequate nutritional status in many paraplegics, the previously reported nitrogen-retaining properties of testosterone[32,33,34] appeared to be highly desirable in this group of patients. Experience in a controlled study with testosterone propionate as a nitrogen-sparing agent in paraplegics indicated that the early use of this drug mitigates the catabolic reaction, decreases nitrogen loss, materially lessens the incidence of decubitus ulcers and improves the nutritional status of paraplegics.[35] Further clinical experience has corroborated this earlier study. Moreover, there is clinical evidence that testosterone improves muscular development in the non-paralyzed upper extremities of paraplegics[36] and enhances their energy and general physiologic and psychologic status.[37] Kochakian et al have reported that testosterone is more effective as an anti-catabolic agent in castrate rats than in normal male rats.[38] Inasmuch as paraplegic males are in effect physiologically castrated, this fact may account for the excellent anticatabolic effects of testosterone in this group of patients.

The value of testosterone therapy in cases of osteoporosis has been well documented by Reifenstein and Albright.[33] Inasmuch as severe osteoporosis, nephrocalcinosis and soft tissue calcification are common in paraplegics, this would appear to constitute another indication for the use of the hormone in cases of spinal cord injury. The effect of testosterone on the osseous atrophy and soft tissue calcifications in paraplegic patients is still being assayed. It is believed that such atrophy in paraplegics is mitigated by the use of steroid hormones. Moreover, Gardner[39] and Halvorsen[40] have reported that the steroid hormones mitigate osseous atrophy in the bones of the extremities that have been experimentally denervated by section of peripheral nerves or hemisection of the spinal cord.

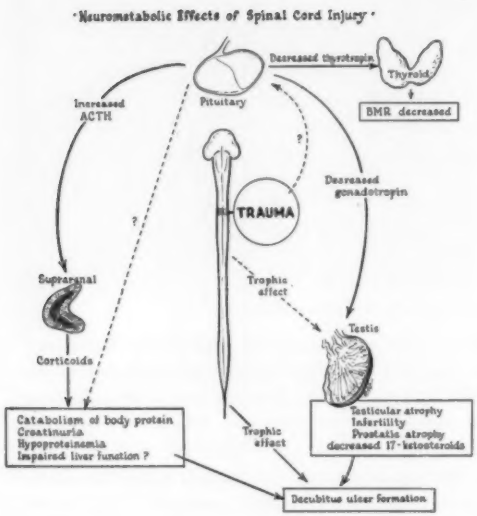

FIG. 3. Schematic representation of working hypothesis concerning pathogenesis of metabolic disorders in paraplegics.

The intramuscular administration of 50 mgm. of testosterone propionate* daily for one month following injury is the most efficacious dosage of this drug following cord trauma. It may then be gradually reduced to 25 mgm. intramuscularly three times weekly. After three months, buccal administration of the hormone is feasible. No masculinizing effects from this dosage in paraplegic females has been observed as yet. In two instances the development of a mild generalized edema was noted while testosterone was being administered; this disappeared on withdrawal of the hormone. Since no other cause for the edema could be elicited, and since testosterone has been reported to cause water and electrolyte retention,[41] it is likely that the edema in this case was caused by the testosterone. No other untowards effects have been noted.

DISCUSSION

It is not the present purpose to speculate at length regarding the pathogenesis of metabolic disorders in paraplegics. Although the thought of grouping the observed metabolic signs and symptoms as a neurometabolic syndrome is an attractive one, the pathologic physiology of these abnormalities is not yet clear enough to permit such a hypothetical categorization. It is obvious that the effects of severe trauma, spinal shock, malnutrition and debilitation, bed rest, chronic infection and other abnormal stimuli may influence the metabolism of paraplegic patients. Therefore, one cannot definitely state that the

*Oreton, supplied by Dr. Edward Henderson of the Schering Corporation.

metabolic consequences of spinal cord trauma are direct consequences of the neurologic lesion, although many of these signs and symptoms are apparently neurogenic. Moreover, it cannot be doubted that the spinal cord lesion has initiated the chain of events producing these abnormalities. A working hypothesis is suggested that many of the early metabolic abnormalities such as the catabolism of body proteins, creatinuria, impaired liver function and a decreased basal metabolic rate are the combined results of the alarm reaction and spinal shock. Later metabolic sequelae such as testicular atrophy, gynecomastia, infertility, prostatic atrophy and altered excretion of the 17-ketosteroids are considered to be primarily neurogenic, as a result of changes produced by transection of the spinal cord. Figure 3 summarizes a working hypothesis of the metabolic effects of spinal cord trauma. Such considerations as the effects of bed rest, genito-urinary infections and a large volume of paralyzed musculature are not included in the diagram. However, this hypothesis is admittedly incomplete and will undoubtedly be modified as factual knowledge of these metabolic disorders is increased.

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It will be perceived that in these cases the true spinal system is affected in proportion to their gravity. To the loss of sense and voluntary motion are now added, dysphagia, stertor, and relaxed sphincters; sometimes there are convulsions, sometimes contraction of the limbs; in other cases, as I have stated, sickness and vomiting.

—Marshall Hall in *Lectures of the Nervous System and Its Diseases*, published in 1876.

Peduncular Hallucinosis Following Vertebral Angiography

J. Rozanski, M.D.

PEDUNCULAR HALLUCINOSIS, a special form of visual hallucinations associated with midbrain lesions, was first described by Lhermitte[1] in 1922. Many remarkable studies on this form of hallucinations have been presented since then, mainly by French neurologists, but have received scant attention in the English literature. The appearance of peduncular hallucinosis as an immediate complication following vertebral angiography has not been recorded previously.

REPORT OF CASE

A married woman aged 34 was referred to the neurological out-patient department on March 6, 1951, complaining of attacks of numbness in the left arm and leg. Her past history was without significance except that at the age of 5 she had been dropped accidentally and suffered head and mouth injuries. It is not known whether she lost consciousness on that occasion. The present disturbance had started five years previously and consisted of attacks of numbness, invariably affecting the left arm or left leg and very often involving both limbs at the same time. The attacks usually occurred at night, lasted from five to ten minutes, and were followed by weakness in the affected extremities. At onset of the disease, attacks were rare and the patient was able to interrupt them by rubbing the numbed member with her healthy hand. During the last four months, however, there had been a gradual increase in frequency of attacks, and two days before consulting the clinic she had noted three attacks in the course of one night. The patient had not lost consciousness nor did she complain of headache, vomiting or vertigo. Her vision, though myopic, was not disturbed.

Clinically, the first diagnostic impression was that the patient was suffering from sensory Jacksonian seizures affecting the left extremities. She was, therefore, admitted to the neurological service for further investigation.

Physical examination: The patient was a well developed woman whose temperature, pulse, respiration and blood pressure were normal. A soft systolic murmur was heard at the apex, but otherwise the physical examination revealed nothing abnormal. Neurological examination disclosed a slight motor weakness in the left leg as compared with the right. The tendon reflexes of the knees and ankles were present and equal. The abdominal reflexes were sluggish. There were no pathological reflexes such as Babinski or Rossolimo.

From the department of neurology of the Hebrew University-Hadassah Medical School, Jerusalem, Israel.

Muscular tone was preserved. Coordination and diadokokinesis were unimpaired. Romberg's sign was negative. No speech disorders were noticed. The superficial sensibility was diminished in the entire left half of the body, including the face. Position and vibration senses and the dermatokinestesis were not impaired. Ophthalmologic examination showed that visual acuity (with spectacles) was 5/6 in the right eye and 5/18 in the left eye. The eye movements were normal. The pupils were round, equal and reacted to light. The peripheral fields were within normal limits. The fundi, apart from a conus inferior in the left eye, were otherwise normal.

Mental examination showed the patient to be mentally normal. She was intelligent, cooperative and lucid; judgment and insight were good and her answers correct. She had not suffered from any mental disease and had never been delirious.

Laboratory findings: The blood count showed a slight leukocytosis with a count of 10,000 per cu. mm. Sedimentation rate was 2 hours 20 minutes (Linzenmeier). Urinalysis revealed a moderate number of white cells. Roentgenograms of the skull and sella turcica were normal. Examination of the spinal fluid disclosed a clear fluid under normal pressure containing a few leukocytes; protein, 12 mgm. per cent; sugar, 58 mgm. per cent; and chlorides, 730 mgm. per cent; Pandy and Nonne reactions were negative; the colloidal gold curve was normal. Wassermann-Kolmer and Kahn tests of the blood and spinal fluid elicited negative reactions. The electroencephalogram revealed a fairly normal pattern. All other laboratory findings were within normal limits.

Course: In view of the development of Jacksonian seizures affecting the left side of the body, a focal process of the right cerebral hemisphere was considered. On March 23 cerebral angiography was performed by percutaneous puncture on the right side of the neck. The solution used was Diodrast in a 35 per cent solution. The object was to fill the carotid artery and thus visualize the intracranial vessels of the right hemisphere. But, as sometimes occurs,[2] the vertebral artery instead of the carotid was filled accidentally, and the films demonstrated the cerebral circulation of the posterior fossa only. At the time of injection the patient complained of a feeling of unpleasantness, and afterwards she noted some most amazing hallucinatory disturbances. Because of their importance her experiences will be presented in the form of a diary which was kept during her hospital stay.

DESCRIPTION OF HALLUCINATIONS

March 24, 1951: Immediately after the examination the patient felt dazed and confused. She experienced nausea and dizziness and did not recognize the door leading to her room. As she got into bed she noticed that her vision was not as clear as usual, and when looking at her husband, she had the illusion that he had four eyes.

When anyone entered the ward, the person was seen double, the second figure being rather vague. The door of a cupboard opposite her bed seemed to rise and fall in continuous movement. From time to time it appeared to her that all objects within her vision were inclined to the right. Later when she tired and closed her eyes, she was surprised by the appearance of different geometric figures like quadrants, zigzags, triangles and cubes, the outlines of which were silver-tinted and intermingled continuously. Only when she opened her eyes did the figures disappear.

Toward evening, as she prepared for sleep and closed her eyes again, she saw lovely pictures. First came a flock of storks with outspread wings, flying along naturally. All appeared in sharp hues as if in technicolor, and she saw very clearly their beaks with little holes in them.

The patient then saw a garden planted with trees and flowers of all colors. The scene was pleasant and the pictures attractive and lovelier than in nature. She was not afraid but was rather astonished and asked herself how such beautiful pictures presented themselves to her. The feeling of nausea recurred and she was obliged to open her eyes. She realized then that she was in a wakeful condition and in full consciousness. She confided to her ward neighbor that she could not understand what was happening to her. She

realized that it was all an abnormal manifestation and was much concerned, but was ashamed to relate that she saw so many vivid pictures lest it be thought that she was inventing them.

Later, when she again closed her eyes, she saw a thickly branched tree against a dark blue background, a grey bird sitting on a bare twig. Quite a number of other nature scenes passed before her eyes until she fell asleep.

In the morning, during the physician's visit, she was asked to close her eyes and to describe clearly what she saw. The patient saw geometric figures, such as quadrants, which turned about in a clockwise direction. Then a green color appeared and transformed the figures into a vague unreality. Nausea recurred and she opened her eyes.

Another neurologic examination revealed that in addition to the left hemihypesthesia and slight motor weakness of the left extremities, present at admission, new signs appeared, namely; diplopia, weakness of convergence, limitation of lateral gaze to the left and dizzy attacks. No other pathologic symptoms were present.

March 25, 1951: The patient appeared to be more accustomed to her condition and not so disturbed. In the evening when she closed her eyes she saw a picture of a Roumanian winter. Snowflakes fell, trees heavily laden with snow appeared and a deep layer of snow covered the earth. The pictures she saw were not framed as in a film but stood out within a setting in a natural surrounding, and the patient felt as if she were part of this scene. Later she experienced a second picture. It seemed as if she were traveling in a train, and as she looked through the window she saw a large field divided into many sections, all of which appeared to be deep green. There were no persons about but from afar there came a white lamb with a red ribbon around its neck. The scene was beautiful and there was nothing in it to terrify her. The third picture was that of a green-covered mountain down which a stream cascaded. She then fell asleep and dreamed no more.

It was difficult for her to describe the pictures she saw as they were so extraordinarily beautiful. She added that if an artist had such experience he would paint brilliant scenes. The patient stated that when she saw the various pictures she wished subconsciously that she could see her children but that was beyond the control of her will.

March 26, 1951: Since the pictures occurred when the patient was about to fall asleep, she avoided closing her eyes during the day. In the evening she was more rested and quietly observed the hallucinations. The pictures changed without the patient opening her eyes. At first she saw a large Persian carpet on which were imprinted multicolored flowers and designs, the colors being dark red, green and white, all very vivid. The carpet kept on revolving and the flowers and designs varied continuously. Then, as in a cinema, the scene changed. A wall of red bricks surrounded a garden, in the middle of which was a running stream of deep blue water. There was a freshness in the garden as after rain.

The patient indicated that she was not so much impressed by the pictures she now saw as by her previous experiences. She wondered, however, how it happened that she, who had never been fanciful and had lived a simple life, should now have such colorful visions.

March 27, 1951: The patient complained of feeling disturbed, just as she might feel coming into a large railway station crowded with people. She was under the impression that her life had changed and that she had undergone an unusual experience. Although fully awake and in her right senses, everything appeared to be dreamlike and all the scenes she had experienced seemed to have occurred a long time ago.

There were moments when her mind was not clear and she could not concentrate on anything. She did not worry about what had happened to her left arm and leg nor was she concerned with her illness. She could not picture her own children. The day before she has held their photographs before her and tried to place them in her consciousness, but it was useless. Her vision was not entirely clear and everything before her was blurred as if she had been gazing into a faulty mirror.

In the evening she again beheld images. The first was a very pretty blue color which was transformed into a water scene. There appeared a wide expanse of sea and on both sides of the horizon there rose high massive mountains. In the midst of this scene the sun began to rise. All these images appeared in colors brighter than nature. Later she observed a flock of white and grey lambs moving slowly along without a shepherd. They did not bleat and all was silent.

March 28, 1951: The nurses noticed that the patient laughed a good deal, was exhilarated and inclined to be jocular. She was in good spirits and felt that her character had changed. Previously she had been interested in her children and worried about what they were eating and if their food was properly cooked. Now she was completely indifferent and had no longing to see them. When her mother visited her she asked about the children out of politeness but the subject did not really interest her and it was as if she were inquiring about strangers. She wondered how she could be so indifferent. "I now have my own world," she said, "and I am not the least bit interested in anything else."

The pictures she had formerly seen at night now came to her during the day. Moreover, she now knew how the images were formed. Closing her eyes she described the following: "From afar I see a darkish-blue color as when the sun sets. Then the color comes nearer and is transformed into a landscape on which is a forest of fir trees." A second experience which she had on closing her eyes she depicted as follows: "I see a green color which dissolves into a field of corn waving gently in the breeze." All day long she saw these pictures and colors and this tired her. The patient was convinced that it was the result of the tests which were being made upon her and she refused to submit to any more of them.

March 29, 1951: The behavior of the patient changed. She began to talk to everyone she saw. In the morning she accused the nurse of being proud but afterwards she wondered why she had behaved thus for she had never hurt people in that way before. She realized that she should not have complained about things that displeased her but she had been unable to control herself. On this day she felt like expressing herself freely, had no respect for others, was unashamed, although she did not know why. She regretted that we had not known her before her illness, when her behavior was natural and simple.

Now she no longer wished to describe the pictures she continued to see during the day. She felt they were part of her personality and asked: "Why should others know about it."

There was no respite from the images which appeared before her uninterruptedly. She was in a jocular mood all the time. "I would willingly sell these pictures to a cinema or even give them away for nothing," she remarked, "but without music and plot nobody would buy them."

March 31, 1951: The patient felt transformed. She was happy, talked volubly, laughed a good deal, was not worried about her children and had become absorbed in her own world. "I have become a merry woman," she remarked.

The pictures did not now come to her during the day but she still saw colors which formed themselves into designs. The colors she saw most frequently were blue, green, white and claret. Red and yellow she seldom saw. The colors formed a circle which began to move in a clockwise direction. Then they rose by themselves and formed a cone, which also revolved. All day the colors were faint but they became more pronounced during the night.

April 2, 1951: The night nurse reported that most of the night the patient sat in the corridor and was reluctant to return to her room. The reason for this was explained by the patient as follows: "Yesterday, when the light was extinguished, I saw colors and designs while my eyes were open. When I closed them I saw a fascinating image: Floating in the air were colored balloons with a rainbow effect. Out of these balloons came showers of smaller balloons in bright colors – green-blue, rose and orange – and all were shining as though there were electric globes inside them." It was a night scene and at first the patient

felt happy, as if she were in a Lunapark. "It was so pleasant," she said, "I began to eat chocolates. That is the custom in a Lunapark. It certainly was not dull and it was indeed a pretty scene." As the images persisted she got out of bed and would not re-enter her room. "I could not sleep. To lie with my eyes open was not interesting and I was tired of seeing pictures with my eyes closed."

April 3, 1951: The patient would not submit to further tests, and at the desire of her family she left the hospital. In the weeks that followed the patient was visited at her home and gradually the situation improved. The psychic condition normalized itself, she was not so moody and her natural modesty returned. The hallucinations also became less frequent.

During her first nights at home she was still subject to vivid visions, but later there were nights when nothing occurred to disturb her. On the other hand, the Jacksonian-like seizures recurred. The patient refused to return to hospital for the completion of the observations and tests.

COMMENT

The most outstanding phenomena in the history of this patient are the visual hallucinations. An analysis shows that they comprise all the characteristic features of so-called peduncular hallucinosis. This separate variety, originally described by Lhermitte, consists of isolated visual images, appearing towards night time as the hour of sleep approaches. The hallucinations usually appear as geometric patterns and designs, or as more elaborate pictures such as landscapes, country and mountain scenes, flowers, birds, animals and sometimes even human beings. The pictures are in vivid, bright colors and are luminous, moving continually in a kaleidoscopic fashion. The affective reaction of the patient is one of pleasure; he looks at his hallucinations with astonishment and amusement, at times even enjoying them. The visions are never associated with fear or anxiety. They are independent of the patient's will and he cannot modify or interrupt them. However, he clearly recognizes the visions as being imaginary and has perfect insight into the hallucinatory quality of his experiences.

As Lhermitte already pointed out in his early works, this form of hallucinosis is always associated with neurologic symptoms indicating lesions of the cerebral peduncles or the immediately adjacent areas in the midbrain. Most prominent are the ocular signs: nystagmus, Parinaud's syndrome, anisocoria, paralysis of lateral gaze, transient diplopia, skew deviation. Frequently there are motor and cerebellar disorders such as hemiparesis, pyramidal signs, dysmetria, ataxia, tremor; at times sensory disturbances are also present. All these signs are quite characteristic of mesocephalic involvement.

This presumption, based on clinical data, was subsequently corroborated by pathological findings. Ludo van Bogaert,[3] at a postmortem examination of a woman aged 59 who had suffered from vesperal hallucinations (animals, colors), observed a softening of the red nucleus, Forel's decussation and the inner part of the cerebral peduncle. In another autopsy Lhermitte, Lévy and Trelles[4] found pigmentary degeneration of the reticular grey matter and degeneration of the oculomotor nuclei.

Lesions of varied natures which affect the mesocephalic region may be responsible for the occurrence of the hallucinations. Lhermitte,[1,5,6,7,8] Lhermitte and Toupet,[9] Lhermitte and Bineau,[10] Van Bogaert[11] and DeMorsier[12,13] reported cases of hallucinosis following cerebral apoplexy in the midbrain due to hemorrhage or thrombosis. Van Bogaert and Delbeke,[14] Alajouanine and Gopcevitch,[15] Garcin and Renard[16] and Albessar[17] described their appearance in infectious diseases of the nervous system, particularly in epidemic encephalitis. Lhermitte and Parturier,[18] Lhermitte and Lévy[19,20] and Trelles and Lagache[21] showed that peduncular hallucinosis can be produced by barbiturate intoxication, since the barbiturates have a special predilection towards localization in the diencephalon. Porta[22] mentioned them in a case of chronic alcoholism accompanied by polioencephalitis hemorrhagica superior of Wernicke. Perria[23] recently observed peduncular hallucinosis in postencephalitic parkinsonism.

How a lesion of the cerebral peduncles, which has no direct connection with the optic center or pathways, could produce hallucinations of a visual character is still not clear. Many explanations have been advanced. According to Lhermitte these hallucinations, produced by lesions located near the hypnic center, are related to sleep mechanism. This interpretation is based on the dissolution theory of Hughlings Jackson who showed that when a higher nervous center is suppressed, the lower centers, normally inhibited, become released and their liberated function appears as a pathologic manifestation. Normal sleep is a physiologic dissolution; during sleep the cortical levels subserving consciousness are out of action, while the lower subcortical levels, being uninhibited, allow the appearance of images, as in dreams. The hypnic function is thus composed of two components: one, positive-dreaming, and the other, negative-suspension of consciousness. In peduncular hallucinosis, according to Lhermitte, the sleep mechanism is dissociated: the dreaming activity is released while the consciousness remains intact or almost so. The hallucinations consequently have the character of wakeful dreams.

Another explanation was advanced by DeMorsier[24] whose conception is essentially organic. In his opinion, peduncular hallucinosis is the result of a lesion in the posterior part of the thalamus, the pulvinar. In support of his theory he cited a necropsy case of visual hallucinations (scenes, landscapes) in which he found large hemorrhagic foci in the posterior part of the thalamus and the right internal capsule. DeMorsier assumes that the pulvinar is relayed to the parieto-occipital cortex through the so-called paravisual central tract, and an irritation of this path may produce a discharge of visual images by stimulating the visual sphere. Lhermitte,[25] however, denies the existence of this path, since the real optic tracts terminate in the external geniculate bodies and are not connected with the pulvinar.

Some neurologists consider that peduncular hallucinosis can be explained by pure psychopathologic concepts of hallucinations in general. According to Van Bogaert, these disturbances may arise from a changed mental state

of the patient characterized by relaxation of the ego, deflection of the sense of reality, modified affectivity, splitting of personality, etc. Baruk[26] does not consider peduncular hallucinosis an independent entity, but rather as forming part of a group designated as "hallucinations oniriques" (dreamlike hallucinations). This variety is encountered in lesions of the base of the brain, the tuber cinereum and also the cerebral peduncles. He takes a critical view of the localizing importance attributed by Lhermitte to the peduncles in the production of the hallucinations.

Recently Alajouanine, Thurel and Durupt[27] likewise adopted a critical attitude toward the conception that this kind of hallucinations was of mesocephalic origin. They report a case of a lower pontile lesion which appeared suddenly after a surgical intervention. The patient developed on one side a peripheral facial paralysis, abducens paresis and Horner's syndrome, and on the opposite side he had hemiparesis of the limbs and hemianesthesia. In addition, he presented hallucinations of a peduncular character. The authors consider these hallucinations to be a secondary product, resulting from diffuse cerebral reaction to various lesions. A pontile lesion may have the same effect on the genesis of the hallucinosis as a peduncular lesion. Therefore they deny any localizing value of peduncular hallucinosis. This assertion, however, is in flagrant contradiction to the many observations recorded by various authors demonstrating the mesocephalic involvement. If, in diffuse cerebral lesions, such as in toxic and infectious processes, it is difficult to ascribe the hallucinations to damage of the midbrain only, it would seem that this correlation is plainly justified in isolated hemorrhagic or softening lesions circumscribed to the mesocephalic area, as shown by clinical data or at necropsy.

To return to the present case, it is noteworthy that no final localizing diagnosis could be made due to the fact that the patient declined any further investigation, in particular air encephalography. Conclusions must be formulated with certain reserve, therefore, though some established facts appear to be very significant. First, there is no doubt that the visual hallucinations experienced by the patient were induced by the vertebral angiography. Their immediate appearance after such a procedure in a woman who was perfectly normal until that time makes this assumption definitely acceptable. Secondly, the variety of hallucinations, as fully described in the case report, is typical of peduncular hallucinosis. In particular, the crepuscular appearance, the panoramic procession of pictures, the pleasant affectivity and the appreciation of their unreality are very characteristic. During the course of hallucinations, moreover, there appeared certain modifications of the patient's mental state. She became euphoric, jocular, slightly disoriented and indifferent towards her family and children. These mental changes persisted only during the period of the hallucinations; later, at home, they receded until they vanished completely. Simultaneous with the psychosensory disturbances described above there appeared some neurologic signs such as diplopia, weakness of

convergence, limitation of lateral gaze and spells of dizziness, indicating mesocephalic involvement. It is our definite impression that the Diodrast injection determined the neurologic signs and provoked the outflow of the visual phenomena by a lesion of the midbrain.

A short survey of the vascular supply of the peduncles may substantiate this hypothesis. The cerebral peduncles receive their blood supply through the peduncular arteries, branches of the posterior cerebral and the superior cerebellar arteries. According to Foix and Hillemand,[28] the superior cerebellar artery gives off one or two arteries to the basis pedunculi and the posterointernal part of the quadrigeminal bodies. From the posterior cerebral spring numerous collaterals, mainly the peripeduncular arteries which supply the peduncles. During vertebral angiography all these arteries, branches of the basilar trunk, were fully injected. It is well known that Diodrast angiography may induce untoward reactions. Chusid, Robinson and Margules-Lavergne[29] have observed the occurrence of transient hemiplegia in two patients immediately following cerebral angiography with Diodrast, and they believe that the clinical manifestations are associated with induced vasospasm of the intracranial vessels. One may be justified in assuming that the peduncular syndrome presented by this patient was also produced by a cerebrovascular spasm in the terminal rami of the peduncular arteries. On the other hand, tiny thrombotic obliterations of the terminal vessels in the midbrain, which may have caused the neurologic signs, cannot be excluded. Finally, the hypothesis that Diodrast acted as a local toxic agent on the midbrain, similar to barbiturate intoxication, may also be advanced. By filling the posterior fossa vessels with Diodrast, this substance arrives in its highest concentration in the mesocephalic area. This favors the localization of the maximum toxicity in the midbrain. The parallelism in the simultaneous appearance of the ocular signs and the visual hallucinations and their concomitant attenuation argues for this view.

At any rate, whatever the origin of these hallucinations, the mere fact that their features tally with the typical pattern of Lhermitte's peduncular hallucinosis and that their appearance followed immediately after vertebral angiography—a sequence of events of which no precedent is known—seems important enough to warrant the present communication.

SUMMARY

Immediately after a vertebral angiography a woman suffering from Jacksonian seizures presented visual hallucinations bearing all the characteristic features of peduncular hallucinosis. The pathogenesis of this variety of hallucinations is discussed.

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Complex as the arrangement of the elements of the brain appears to us to be, it may be found, with fuller knowledge, that the principles of the plan are comparatively simple. The variety in form of the nerve-elements is small, if we consider how numerous they are. The fibres present little variation. The cells, even when the element of size is taken into consideration, may probably be classed in not more than a dozen varieties. It is the arrangement and connection of these elements that constitutes the complexity of structure of the brain, and subserves its complexity of function.

Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Neurology

Clinical Pathologic Conference

From the Department of Neurology, University of Michigan Medical School, and University Hospital, Ann Arbor, Michigan

Presented by Russell DeJong, M.D. and Konstantin Scharenberg, M.D.

PRESENTATION OF CASE

A 38 year old colored male crane operator was admitted to the University Hospital on December 19, 1951, complaining of spells of generalized "numbness" after meals for five months, and "drawing" pains in the head and severe dizzy spells for three weeks. Two generalized convulsions occurred the week of admission.

History: At the age of 17 the patient injured his neck while diving; he stated that he had sustained a fracture of the cervical spine but was not hospitalized. Following this accident he had severe hiccoughing, dysphagia and blurring of vision for two to three weeks. Dysphagia had recurred on occasion from that time on. He also stated that he had had some clumsiness in the left hand for many years and had frequently burned this hand. He volunteered the information that he had been impotent for many years and recently had been entirely unable to ejaculate.

Five months before admission he began having more dysphagia, indigestion, flatulence, and transitory generalized numbness which came on with meals and disappeared a few hours after. These attacks continued until three weeks prior to admission, when he began complaining of pain in the head. This he described as a drawing or pressing sensation in the frontal regions, bilaterally, which caused diplopia and dizziness. Tinnitus was associated with the pain. Ten days before hospitalization the patient had a severe dizzy spell with marked tinnitus, which caused him to stay home from work for two days. He then returned to work, but had a dizzy spell shortly before noon. He drove home and went to bed, and shortly afterward his wife found him lying on the floor, frothing at the mouth and "stiff as a poker." He was taken to another hospital where he remained unconscious for 17 hours, waking suddenly while x-rays of the skull were being taken. He was apparently wide awake, clear and coherent at that time. Following this he became somewhat drowsy and lethargic and remained so until entrance to this hospital. He also complained of marked difficulty in vision which was improved by shutting one eye. Ringing and buzzing sounds had occurred in the left ear during the week immedately preceding admission. Both the patient and his family had noted impairment in his memory for recent events. One day prior to admission, while sitting on the toilet attempting to defecate, he lost consciousness, became limp, exhibited profuse diaphoresis, and urinated involutarily. He remained unconscious for ten minutes.

Physical examination: The patient was quite drowsy and lethargic but responded readily and was entirely cooperative. There was definite impairment in recent memory, and many of the details concerning the present illness were elicited from his wife and family. His temperature was 98.6°; blood pressure, 130/75; pulse rate, 76, and respirations, 16 per minute. The general physical examination was unremarkable except for a marked macular eruption over the arms, chest and back with many scars and keloids of the hands and arms which the patient said had resulted from burns that had never caused him discomfort.

Neurologic examination: He was unable to distinguish any of the usual test odors. The pupils were round, regular and equal, reacting well to light and in accommodation. Ophthalmoscopic examination revealed only slight gliosis of the vessels below the left disc. Visual acuity was correctible to 6/9-2 bilaterally. Perimeter and tangent screen visual fields were normal. The blind spots were not enlarged. There was a constant red glass diplopia which was equal in all directions of gaze. An intermittent divergent strabismus was noted and a Lancaster test suggested a concomitant difficulty with weakness of no particular muscle. There was a coarse lateral nystagmus with some rotary component bilaterally. Vertical nystagmus was noted on several occasions. There was no motor weakness of either the masseter or ptyregoid muscles. Facial sensation, including that of the cornea and nostril, was intact. The muscles innervated by the seventh cranial nerve showed no weakness. Audiometric studies were normal. The gag reflex was present bilaterally, and the uvula moved upward in the midline. The muscles supplied by the accessory nerve were normal in function, and the tongue protruded in the midline, without atrophy or fibrillations. Motor examination revealed only a minimal paresis of the left upper extremity; there was no atrophy. Reflexes were overactive but equal in both upper extremities. The reflexes in the lower extremities were normal. The superficial abdominal reflexes were absent. There was a Babinski sign on the right. There was slight dysdiadokokinesis of the left upper extremity, but all the other tests of coordination were normally performed. The sensory examination revealed a dissociated sensory change from C_2 to D_{11} bilaterally with analgesia and loss of temperature sensation but with intact touch, position, vibration and deep pain sensations. There was also loss of appreciation of heat and a hypalgesia in $S_{3,5}$ segments.

Laboratory examination: The routine blood count and urinalysis were normal. The blood Kahn test was negative. Lumbar puncture: initial pressure, 200 mm.; fluid, clear; 4 lymphocytes per cu. mm.; Pandy, negative; total protein, 47 mg. per cent. The spinal fluid Kahn was negative. X-ray of the skull showed no evidence of abnormality; the pineal was not calcified, but there was calcification in the choroid plexus bilaterally. There were marked hypertrophic changes involving the fourth to seventh cervical vertebrae, with a decrease in the intervertebral disc space between C_6 and C_7. There was hypertrophic encroachment on the neural foramen at the level of C_5 on the left. X-ray of the chest was normal. Cystometric studies revealed normal detrusor function but complete loss of temperature perception in the bladder. A quinizarin sweat test showed loss of sweating over the entire left side of the face and in the C_2 and C_3 segments on the left. An electroencephalogram showed a paroxysmal pattern without significant evidence of a localized lesion.

Course in the hospital: On the fifteenth hospital day a ventriculogram was performed. A space occupying lesion lying deep in the right thalamic region was demonstrated. A craniotomy was done, but no definite tumor tissue could be identified. An internal decompression was performed, but the patient remained in coma and expired with a markedly elevated temperature on the eighteenth postoperative day.

DISCUSSION

DR. DEJONG: From an anatomic point of view, this man appears to have had intramedullary disease of the spinal cord and possibly the lower brain stem. The dissociated sensory findings in the upper extremities point strongly toward an intramedullary spinal cord lesion. The finding of dissociated sensory loss in the sacral segments suggests involvement in this area of the cord as well. From the point of view of history it appears that this patient had burned himself over quite a long period of time. We are not told at precisely what age he began to

notice these non-painful burns. Whether this manifestation dates from the time of the supposed cervical spine fracture or whether it antedates that, we do not know. The patient's history of impotence goes back 15 years or so according to his story. This again suggests a long-standing chronic cord condition. Evidence pointing to involvement of the lower brain stem is chiefly historical, but I think we may accept as accurate his story of hiccoughing and continued mild difficulty in swallowing. The patient dated these symptoms to the time of his diving accident. The routine neurologic examination failed to show any evidence of lower brain stem disease, but the sweat tests indicated involvement of some of the fibers of the trigeminal nerve.

I think then that we have anatomic and historical evidence of long-standing intramedullary disease of the spinal cord and possibly the lower brain stem. Whether this involvement is secondary to the spine injury which occurred in the patient's youth, or whether it represents a process that has been present for many years, even antedating the accident, is hard to determine.

The acute situation which led to hospitalization indicates the presence of an intracranial lesion. The patient had had true convulsive seizures, and he had been lethargic and showed impairment in memory. Is the recent clinical picture which led to his hospitalization the result of an extension of the apparently older pathologic process, or is it entirely unrelated? The assumption that it is entirely unrelated leads to a double diagnosis, usually to be avoided. On the other hand it seems very hard to relate this long-standing history of intramedullary cord disease to the immediate situation. If, as could be argued, the sensory findings were the result of the trauma to the neck, then we have little or no reason to expect that process to continue or to progress and cause grand mal seizures with lethargy, impairment of memory and drowsiness. If, on the other hand, we ignore the possible relationship between trauma and cord pathology, we are faced with the problem of just what type of chronic cord lesion would progress and lead to the present acute illness. Of course syringomyelia is a strong possibility on the basis of the sensory findings. It has been reported that syringomyelia and convulsions are at times associated. On the other hand, if this is a syringomyelia and there has been progression, it must have been upward extension. We found no evidence of involvement of the bulb other than the sweat test and the history of occasional difficulty in swallowing. It seems unlikely that impairment of memory and drowsiness and lethargy could be caused by extension of the syringomyelic cavity unless there were other neurologic involvement pointing to disease of the brain stem proper.

I feel then that we are dealing with two separate pathologic processes. One of these is probably a long-standing syringomyelia involving the cervical and possibly the sacral segments of the cord as well as the medulla. The other lesion is an intracranial one unrelated to the syringomyelia.

There is nothing in the history or physical examination which enables us to localize this intracranial lesion. The fact that there had been progressive drowsiness and lethargy suggests either a frontal lesion or else an expanding one causing diffuse pressure. We have little evidence of diffuse pressure, except the mildly elevated spinal fluid pressure. There was no papilledema. The nystagmus could be interpreted as due to diffuse pressure, or perhaps as a localizing sign pointing to a lesion involving pathways in the upper brain stem. Nystagmus such as this man showed is not frequent in diffuse intracranial pressure. This nystagmus probably represents involvement of the upper brain stem and periaqueductal region and is perhaps of localizing significance. We cannot, however, rule out the possibility of this nystagmus being related to the syringomyelia and syringobulbia which we have diagnosed.

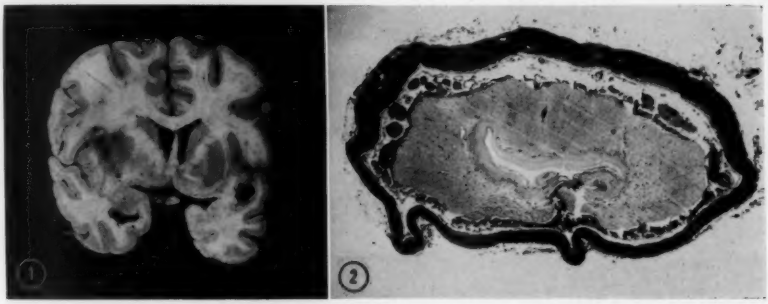

FIG. 1. Coronal section through the striate body showing a large granuloma in the insula and the putamen on the right. FIG. 2. Eighth cervical segment with a typical syrinx and thickened meninges. Azan stain.

We are told that this patient had difficulty in distinguishing the test objects for smell. We have not been told whether or not he recognized the fact he was smelling different odors or whether he simply could not name the odors. If he was unable to name the odors, I am inclined to dismiss the reported difficulty in smell as being insignificant. If he was unable to tell that he was smelling different odors, then I think we must consider anosmia as a positive finding and must make some explanation for it. The anosmia was bilateral, and we do not know its duration. Assuming the anosmia was real, we can only say it points to localization in the anterior fossa. I am inclined to feel that the anosmia has no particular significance in regard to localization of his lesion. An attempt to relate the anosmia, if it really exists, to the syringomyelia is even more difficult. It has been pointed out that anosmia is not infrequent in syphilis of the central nervous system. There are some who believe syringomyelia may be on a luetic basis, and possibly this is the case here despite the lack of serologic evidence of syphilis. I doubt that this is true and prefer to assume the anosmia to be of no significance in this particular case.

I believe that, in addition to the spinal cord condition, we are dealing with an expanding intracranial process which I cannot localize except for the reported ventriculographic evidence of a deep right hemispheric lesion. The nature of this process has now to be considered. In a man of this age with a recent onset of headaches, vertigo and convulsions, we are of course extremely suspicious of a brain tumor. We have nothing in the general physical examination or the x-rays of the chest to suggest that this is a metastatic neoplasm. There is nothing in either the history, the physical or the laboratory examination to indicate that we are dealing with a pyogenic process or brain abscess.

In summary then, I would make a double diagnosis. I believe this man was suffering from a syringomyelia and also from an unrelated, expanding intracranial lesion which I cannot localize from the data I have been given, except to rely on the evidence from the ventriculogram that it is deep in the right hemisphere. I believe the neoplasm is a primary brain tumor rather than a metastatic one.

CLINICAL DIAGNOSIS: (1) *Syringomyelia.* (2) *Primary brain tumor, unlocalized, probably deep in the right cerebral hemisphere.*

PATHOLOGIC DISCUSSION

DR. SCHARENBERG: The brain showed marked enlargement of the right hem-

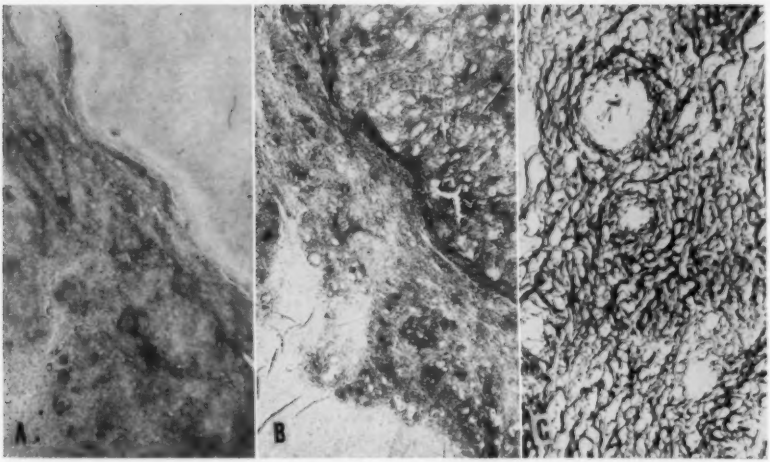

Fig. 3. A. Caseated area of the granuloma (upper right segment of the picture). v. Gieson stain. B. Connective tissue network in the necrotic area (low power). Silver carbonate. C. Connective tissue network of the same area at higher power. Silver carbonate.

isphere. As a result of the recently performed internal decompression a conical defect of the brain substance in the right temporo-parietal region existed. The surface of the wound was covered with hemorrhagic debris. The defect extended to the medial part of the thalamus. There was no evidence of meningitis. The basilar arteries were not sclerotic.

Coronal sections revealed a spherical lesion approximately 25 cm. in diameter between the insula and the anterior limb of the internal capsule on the right. It was reddish gray in color and hard in consistency. The surrounding brain tissue was edematous (figure 1).

Cross sections of the spinal cord demonstrated cavity formation extending from the upper cervical cord to the lower part of the dorsal region. Histologically the cavity was lined mainly by proliferated glial tissue and some connective tissue fibers arising from the vessels. The cavity was located dorsal to the central canal (figure 2). It represented a true syrinx as demonstrated by the glial lining and the location of the cavity.

On histologic examination the lesion in the brain was demonstrated to be a granuloma with a large area of central necrosis in which silver carbonate preparations demonstrated a dense network of connective tissue fibers (figure 3). Special preparations revealed also a great number of elastic fibers. There were shadows of numerous vessels which have been thrombosed. In the marginal zone of the granuloma there was marked increase in the number of the vessels and proliferation of their walls with widespread formation of interstitial connective tissue which served as a skelton for numerous small granulomas built of epitheloid and giant cells of the Langhans type. Some vessels showed perivascular cuffing with lymphocytes and plasma cells. Occasionally their elastica interna was hypertrophic and was split into several layers. The lesion extended from the insula across the subarachnoid space into the adjacent area of the operculum, producing a circumscribed

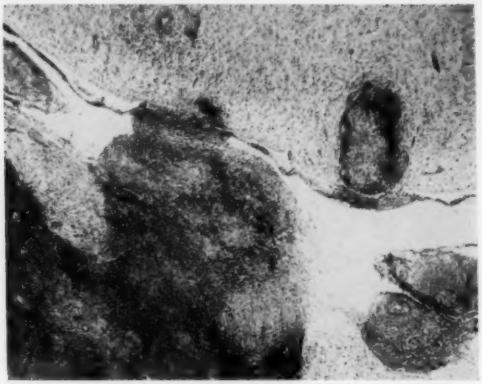

FIG. 4. Extension of the granuloma into opposite convolution with invasion of the meninges and formation of two small granulomas. v. Gieson stain.

meningeal reaction and contributing to the formation of additional granulomas (figure 4).

The etiology of the lesion is not clear. Histologically it demonstrated certain features of gumma. However, examinations of the spinal fluid and the blood were negative for syphilis. Special stains (Jahnel) revealed no spirochetes. Tuberculosis is the other possible etiologic factor. This is suggested by the presence of epithelioid and giant cells and by caseated lymph nodes found at the bifurcation of the trachea. However, acid fast bacilli were not demonstrated in the granuloma, so that the etiology remains in some doubt.

This case is of interest because it shows two etiologically different, independent lesions of the central nervous system, the symptoms of which were correctly interpreted and were satisfactorily explained by the pathologic findings.

PATHOLOGICAL DIAGNOSIS: (1) *Syringomyelia.* (2) *Etiologically obscure granuloma of the right cerebral hemisphere, probably tuberculoma.*

The experimental researches on the functions of the brain, chiefly of Hitzig and Munk in Germany, and Ferrier in this country, have also given us vast help in diagnosis. Here also, however, we meet with contradictions; and here also more has been ascertained than we can at present apply. Our guide in this department must be the facts of clinical and pathological observation. We must beware of applying wholesale to the human brain the conclusions derived from experiments on animals. The latter are of value to us only as indications for observation on man, and by enabling us to give a fuller interpretation to the facts we learn by our study of disease during life and after death. Some of the experimental facts have at present received no confirmation, and on some points we especially need information, which, from their nature, experiment cannot give.

—Sir William R. Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord,* published in 1885.

Case Report

Vertebral Artery Aneurysm

Marcus Bushard, M.D., Eric Yuhl, M.D. and Ralph W. Barris, M.D.

Cruveilhier[1] in 1835 was the first to report a case of aneurysm of the vertebral artery. Seventy-two additional cases were recorded in the literature up to 1944. Occasional case reports have been published since that time. In the case to be reported here, clinical history implied the existence of neurologic signs referable to the vertebral aneurysm over a period of 40 years prior to death.

CASE HISTORY

A 60 year old white male, a missionary to China for the previous 28 years, was admitted to the hospital on September 9, 1950, with chief complaint of pain in abdomen of five days' duration, followed by generalized abdominal tenderness and localized pain in right lower quadrant, with associated nausea and vomiting. A diagnosis of acute appendicitis was made and an operation performed; appendiceal suppuration with rupture was noted, and drainage was instituted. The postoperative course was uneventful. Neurologic consultation was then requested because of a rather vague history of right upper and lower extremity weakness and a subjective complaint of "dizziness."

Inquiry revealed a 40 pound weight loss and easy fatigability during the past year, attributed by the patient to a poor diet and severe recurrent bouts of diarrhea while in China. He had also been aware of a progressive weakness of the right lower extremity during the past year, and in the past few months of progressive and more severe weakness of the right upper extremity. In addition he had noted an intermittent "dizziness," relatively persistent during the past three months, and an associated unsteadiness when walking. He stated that he had been troubled with headaches all his life, usually suboccipital and greatly increased in severity and persistence during the past few months, at times during the past few weeks interfering with sleep at night. He had also noted that these headaches were either initiated or exaggerated by straining at stool. During the past month he had noted a tendency towards vomiting without associated or antecedent nausea, the last episode occurring just before breakfast. During the past month he had been troubled with increasing bouts of hiccoughing. Swallowing had become progressively more difficult and hoarseness and weakness of speech had become evident during the past three months. His past history revealed that about 40 years previously he had noted a sudden severe "snapping" pain in the left parietal region, associated with a paralysis of the left side of the face, a low-grade left facial paralysis persisting since that time.

From the Veterans Administration Center, Los Angeles, California.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own studies and do not necessarily reflect the opinion or policies of the Veterans Administration.

Six years and three years prior to present illness, respectively, he had experienced sudden onset of left sided headaches, for which on the latter occasion he was hospitalized for one week.

Neurologic examination revealed a somewhat emaciated male, oriented, relevant and coherent. Blood pressure was 160/90. Speech was characterized by a hoarseness and weakness but was not slurred. The uvula deviated to the right and the palate on the left failed to contract on phonation; gag reflex was absent on the left. Mirror laryngoscopy revealed a paralytic left vocal cord. The left nasolabial fold was flattened. A fine, rhythmic, horizontal nystagmus was noted on looking to the right or left, about equal on the two sides. Swallowing difficulties were evident, with at times a tendency to choke while eating. The motor functions of the right extremities were impaired, the arm greater than the leg, and there was a moderate atrophy of the muscles of the right shoulder girdle with moderate "winging" on voluntary protraction and abduction of the right arm at the shoulder. A palpable mass about 1½ cm. in length, pulsating, in the course of the right popliteal artery was noted and thought to be an arterial aneurysm. The deep reflexes were reduced on the right as compared with the left, being absent on percussion of the right biceps tendon and barely perceptible and sluggish in the remainder of the right extremities. On the left side the biceps reflex was sluggish and barely perceptible, but all other reflexes were easily elicited and approximately uniform in upper and lower extremities. Abdominal and cremasteric reflexes were intact. No pathologic reflexes were obtainable. The right extremities were hypotonic as compared with the left. The gait was broad-based, dystaxic, with a tendency to veer to the left. Heel to knee test poorly performed on the right with dysmetria. Romberg test revealed swaying of about equal degree with eyes opened or closed. Sensory examination revealed no abnormalities.

Clinical course: The above neurological findings suggested involvement of the brain stem and cranial nerves in the left posterior fossa, but at no time was the diagnosis of arterial aneurysm entertained. The spinal fluid at the time of the first neurologic evaluation was clear with an initial pressure of 140 mm. of water, 2 lymphocytes, 1 plus globulin, negative Wassermann, 126 mg. of protein, and gold curve, 4444321100. Spinal fluid cultures on Sabouraud's and routine media were negative. The differential diagnoses included nasopharyngeal carcinoma with metastatic invasion, schistosomiasis with granulomatous involvement of the basilar meninges, meningioma, meningeal carcinomatoses, malignant lymphoma, multiple myeloma, and granulomatous mycotic meningeal invasion. Many of these possibilities were eliminated by further studies, the upper and lower gastrointestinal x-rays being normal, as were the intravenous pyelograms and x-rays of the skull, spine and chest. Sternal marrow biopsy and x-rays of the skull, spine and chest. Sternal marrow biopsy was negative and no Bence-Jones protein was found in the urine. The routine blood and urine studies were within normal limits except for 2 plus albumin in urine; serum phosphatase and inorganic phosphorus were normal. Stool studies were negative for ova, parasites and occult blood, and sigmoidoscopy revealed nothing abnormal. The electroencephalogram was interpreted as mixed S_1F_1 record during both waking and sleep.

Progression of the neurologic disability was observed. Outstanding were the progressive dysphagia with tendency to choking, periods of intractable hiccoughing, intermittent spontaneous vomiting often precipitated by turning of head to right, subjective dizziness, increased hoarseness and weakness of speech, and progressive weakness of right arm and leg, the former greater than the latter. It was decided that ventriculograms might be of value in determining evidences of a possible coexisting obstructive hydrocephalus, inasmuch as pneumoencephalography failed to reveal the presence of air in the ventricular system, even though subarachnoid air accumulation appeared normal. Ventriculograms revealed normal lateral ventricles, without shift, the third ventricle being slightly enlarged and in the mid-line. In one lateral view, air was demonstrated in the fourth ventricle.

Left posterior fossa exploration was being contemplated on December 12, 1950, on which date the patient expired rather suddenly following an intravenous infusion of protein hydrolysate solution, with signs thought to be due to acute medullary failure (weak, rapid, and irregular pulse; irregular and shallow respiration; falling blood pressure; and rapidly developing coma).

FIG. 1. Aneurysm is shown involving the left vertebral artery. Note the distortion and compression of the brain stem and inferior surface of the left cerebellum.

Necropsy: As illustrated in figure 1, a large aneurysmal dilation of the left vertebral artery, with marked distortion and displacement of the brain stem and left inferior cerebellum, was discovered. There was an excessive tortuosity of the basilar artery as well as of the right and left vertebral arteries. Additional autopsy findings revealed evidences of congestive heart failure, "old" myocardial infarction, and generalized arteriosclerosis. A popliteal artery aneurysm measuring 1 by 2 cm. was noted on the right.

DISCUSSION

The existence of a popliteal and vertebral artery aneurysm in this patient together with a history of sudden onset of left facial paralysis and acute left sided head pain 40 years prior to the gradual development of neurologic signs suggesting involvement of the left brain stem appears compatible with a congenital origin for the aneurysm described herein. The rarity of vertebral artery aneurysms is attested to by statistical analysis by McDonald and Korb[2] of 407 reports in the literature which revealed that out of 1023 cases of intracranial aneurysm, only 59 were of the vertebral type, less than six per cent of the total. In Dandy's[3] series of 133 verified intracranial aneurysms, only two were of the vertebral type. Robertson[4] found not a single case of vertebral aneurysm in 93 cases of intracranial aneurysm examined at autopsy. A review of the literature confirms that vertebral artery aneurysm like other intracranial aneurysms may remain silent throughout life, that sudden subarachnoid hemorrhage with or without coma and death may occur, or that progressive or sudden localizing neurologic signs may reveal the existence of the vertebral aneurysm. These latter symptoms include headache, dysarthria, dysphonia, dysphagia, nausea, vomiting, syncopal attacks and hemiparesis. Dandy[3] has emphasized bilateral motor signs and symptoms as being strongly suggestive. Yaskin and Alpers[1] have stressed the importance of frequent tonic cerebellar states and transient cranial nerve palsies. Vertebral angiography probably represents the best current diagnostic aid. Sugar et al[5] reported a high percentage (75 per cent)

of successful vertebral angiograms with a minimum of complications. In the case presented here, necropsy revealed extensive thrombosis of the left vertebral artery aneurysm. Vertebral angiography might have, none the less, demonstrated the abnormality.

SUMMARY

A case of left vertebral artery aneurysm, probably congenital, has been presented. While the history suggested its presence approximately 40 years prior to death, it was not diagnosed until necropsy.

The coexistence of a popliteal artery aneurysm in this case makes the presumption of congenital origin more impressive.

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Headache is, of all the many symptoms that organic disease may produce, the most distressing; and at the same time the most equivocal, the most apt to mislead both the patient and the physician. Local pain is a symptom of universal incidence; wherever it occurs, it absorbs the attention of the sufferer, and to him at least, suggests irresistibility a local cause. But of all seats of pain, the head is the most common, and pain is here the most suggestive of local disease. In consequence of some mysterious relation, pain in the head is the common result of most varied causes—of stomach disturbance, of anaemia and plethora, of every kind of morbid change in the blood, febrile conditions, acute specific diseases, kidney disease, toxaemia. The nerves that supply the walls of the skull are prone to neuralgic pain of every kind. Headache occurs also in various functional disorders of the nervous system. It readily results from mechanical congestion of the brain, however produced, and is sometimes so obtrusive that the patient notices the cause less than the effect. Thus I have known a patient to come for treatment on account of headache, and to complain of nothing else, when the headache was the result of cough, and the cough of phthisis. I think it is no exaggeration to say that for one case of headache due to organic disease of the brain, you will meet with fifty that are due to other causes.

—Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published 1885

Neurology

R. Foster Kennedy, M.D., 1884-1952

Dr. Foster Kennedy died on his own ward in Bellevue Hospital, New York City on January 7, 1952, following an intestinal hemorrhage. This resulted from periarteritis nodosa which had caused him much distress during the last year of his life.

Born in Belfast, Ireland, he would have been 68 years old on February 7. Dr. Kennedy came to New York from London in the summer of 1910 after four years of study at the National Hospital, Queen Square. There he was fortunate enough to serve under such able clinicians as Sir William Gowers, Hughlings Jackson, Sir Victor Horsley and Sir Henry Head.

He was invited by the late Dr. Pearce Bailey to come to the then recently founded New York Neurological Institute, where he continued his work for many years.

Soon after World War I broke out in 1914, Dr. Kennedy went to France. He had many narrow escapes from death in the front line and he added much to his knowledge of nervous diseases. In 1918 he published a paper "The Nature of Nervousness in Soldiers," an illuminating exposition of hysteria. Dr. Kennedy was the first to point out that shell shock is hysteria, and its various forms arise from the insoluble conflict between the soldier's instinct for self-preservation and his herd instinct. In this paper Dr. Kennedy took issue with Freud and said: "The tremendous mass of material made available by war demonstrates the general rightness of this principle (i. e., that neurotic symptoms may be produced by the antagonism of mutually incompatible emotional trends) but still more definitely proves the peculiar wrongness of the details with which the psychoanalysts have applied it and entirely invalidates their deduction – elaborate as a pontifical dogma – that the sexual instinct . . . is the only dynamic force possibly concerned."

One of Dr. Kennedy's contributions to thought in our time has been his persistent demonstration that when a man is mentally ill he has something wrong with his brain. This principle has not been accepted as an axiom by psychiatrists. However, environment is not the only factor in the emergence of a psychosis, although it may be important in the development of a psychoneurosis such as hysteria. Dr. Kennedy referred to this in his paper "Functional Nervous Disorders in the Last War, the Spanish War, and Now," published in June 1943. Here he stated "Mira's experience in finding no more psychoses occurring in the Spanish War than in peace time is identical with the experience of the First World War. There were more neuroses but no more psychoses." Dr. Kennedy's conviction was that the solution of the problems of mental illness would never come from the analyst's couch.

On his return from France, Dr. Kennedy soon found himself in the middle of the great epidemic of encephalitis or, as it was more commonly known, sleeping sickness. By the end of 1919 his wards were filling up with acute cases of this disease. A series of papers followed as a result of his studies, the first one in 1919 entitled "Epidemic Encephalitis with Stupor" – the last one in 1933 entitled "Narcolepsy." Many types of this disease were first described by Dr. Kennedy. Of great importance to every physician is his paper "Acute Benign Meningo-Encephalitis with Papilloedema" published in 1922. In 1930 his paper "The Relationship Between Mind and Brain in the Light of Epidemic Encephalitis" goes a long way in helping us to understand mental illness.

Others among his published papers are "Traumatic Neurosis" (1922), and "Epilepsy and the Convulsive State" (1923). Papers on brain tumors described what is now known universally as "The Foster Kennedy Syndrome," a combination of neurologic signs and symptoms diagnostic of tumors of the frontal lobe of the brain. In 1925 there was an account of the first use of Tryparsamide in this country for the treatment of syphilis of the nervous system. Like most neurologists, Dr. Kennedy had much to do with epilepsy and described some of the most illuminating cases in the literature.

In 1926 he wrote a paper "Cerebral Symptoms Induced by Angioneurotic Edema." In some of his patients Dr. Kennedy found evidence of swellings in the brain or in certain parts of it like the optic nerve. Since then he had written several papers on this subject; for example, "Allergic Manifestations in the Nervous System" in 1936. This was a courageous thing to do in 1926 or even ten years later, for allergy was then looked upon with suspicion as a cause of nervous disease.

One of Dr. Kennedy's most important original contributions to neurology was his paper on "The Symptomatology of Temporo-Sphenoidal Tumors" written in 1911, and other papers on this subject as late as 1932. Dr. Kennedy's war experience, added to later experience at Bellevue, has led to important knowledge about the functions of the brain and, in particular, the cerebral cortex. He described repeatedly cases where a small wound or a small tumor had injured the cortex of the brain in a very circumscribed area, destroying only a fragment of the patient's cerebral function. One of the most fascinating cases of this type he told about in "The Organic Background of Mind" delivered at the New York Academy of Medicine in 1936: "We had in Bellevue Hospital . . . a young woman who by taxicab accident had sustained an injury to the left side of her head. From this there came a slight weakness of the right arm which entirely passed off in a week or two. Six or seven weeks after the injury . . . . I saw her and learnt from her that she had been an honor student at the National School of Design. I asked her, therefore, to draw a face for me. She said, "Of course, yes." She took pencil and drew a face consisting of a circle, two dots, a vertical dash and a horizontal. And I said, "Is that the best kind of face you can draw?" She was much troubled by her ineptitude, which she had not anticipated, for she could not put her pencil to drawing any better kind of face than would have been drawn by a child of four or five. Each day we had her draw, and almost every day we saw flow and economy coming into her lines. In two or three months she drew again as well as she had drawn before her injury. The hurt sustained to the hand center in the brain had deprived her of an educated faculty, the translation of design. . ."

Dr. Kennedy was a pioneer in the use of electro-shock therapy in the treatment of psychosis and had remarkable success with it as a physiological means of altering or curing disease of the mind.

In 1940 he was elected president of the American Neurological Association. In 1950 he received the honorary degree of D. Sc. from Queen's University, Bel-

fast, where he graduated in medicine in 1906. He had been honored by the governments of France and Cuba as well as Great Britain and the United States. He was a Fellow of the Royal Society of Edinburgh. At the time of his death he was professor of clinical medicine (neurology) at Cornell and had been director of the neurological division of Bellevue Hospital from 1915 until his retirement in 1949. He was consulting neurologist to the New York and Memorial Hospitals and consulting physician to Bellevue. He will be longest remembered, however, by those happy young men and women who through 34 years followed him in their rounds as his resident medical officers at Bellevue.

Having read all of his writings, you must then have walked his wards at Bellevue with him — you must have seen him slip a few dollars into the hands of a penniless patient from the lower East Side by way of prescription for his ills — and you must have enjoyed the hospitality of his home — in order to understand his greatness.

With Dr. Kennedy's death we come to the end of a colorful era in American medicine. His illustrious contemporaries have disappeared from the scene one by one, and few remain. The roster of the Charaka Club will bring to mind many of his companions who were poets and philosophers as well as healers of the sick. To all he was known as one of the leading personalities of his time, and, to some of us, as a generous and constant friend.

LEWIS D. STEVENSON, M.D.

Neurology

BOOK REVIEWS

A History of Neurological Surgery

Edited by A. Earl Walker, M.D. 1951. Baltimore: The Williams & Wilkins Company. 583 pages, $12.00.

Members of the division of neurological surgery at the Johns Hopkins University, under the guidance and editorial direction of Dr. A. Earl Walker, have presented to those interested in their own and related specialties an encyclopedic historical survey. Starting with a discussion of prehistoric and primitive trepanation, the development of neurology and neurologic surgery are reviewed up to the present time.

As is often the case in volumes in which individual chapters are written by different authors, the discussion of some subjects is more complete and more interestingly presented than that of others, but throughout the entire book one can gather that the editor has attempted to make the presentation as even as possible.

The neurologist may regret that greater stress has been given to technical development of surgical procedures than to the diagnosis and the evolution of anatomic and physiologic concepts, but as a result of this stress on technique, the medical neurologist is given better insight into the problems and goals of his surgical colleague. The chapter which will have the most interest for the neurologist, and perhaps the best-written section, is that by Dr. Walker himself on "Diagnostic Procedures." Herein is related the historical development of spinal fluid examination, neuroroentgenology, ventriculography, pneumoencephalography, angiography, myelography and electroencephalography.

Of special interest in the book is a series of brief biographical sketches of prominent neurosurgeons.

The only major criticism of the book is that in an attempt to present a fairly complete historical survey, the authors have at times given only cursory mention to the contributions of certain outstanding contemporary neurosurgeons, and though many names are listed in the history of the various fields, adequate stress has not been given to those men who were responsible for major developments. Another criticism is directed toward the manner of calling attention to the more than two thousand books and articles cited in the bibliography; the reference citations are placed in parentheses after the names of the authors in the text, and the reader is often confused and misinterprets reference numbers for dates.

In spite of these criticisms, however, one must state most definitely that Dr. Walker and his associates have contributed a comprehensive, fascinating, much-needed historical survey of neurologic surgery that every neurologist as well as every neurosurgeon should have at his finger tips. R. N. DE J.

The Normal Cerebral Angiogram

Arthur Ecker, M.D. 1951. Springfield, Illinois: Charles C Thomas, Publisher. 216 pages, $6.50.

Cerebral angiography has been universally accepted as an important roentgenographic method for the diagnosis of intracranial lesions. This book, therefore, is timely and fulfills a real need. It is, incidentally, the first monograph on the subject written by an American author. Dr. Ecker is an enthusiastic proponent of angiography and has large personal experience with it.

The first part of the book is primarily written for beginners and deals with the technique of angiography describing in minute detail the percutaneous techniques as used by the author. Many of the pitfalls and complications are mentioned and explicit suggestions given for avoiding them. This first part of the book is excellent, yet in a monograph of this scope one misses reference to techniques employed by other authors and particularly a discussion of the still controversial problem of contrast media.

The second part of the book is devoted to the normal angiographic anatomy as demonstrated on carotid and vertebral angiograms. Multiple and unusual projections are used (e.g. oblique orbital views) to show the vessels to a better advantage. An instructive chapter deals with the description of artifacts resulting from faulty technique of injection or from inaccurate roentgenographic positioning.

In a final section, the topographic relationship of the basal vessels to the slit of the tentorium and foramen magnum is investigated both in normal individuals and cases of intracranial tumor.

The second half of the monograph would gain much in clarity and didactic value by a condensation of the text and more correlated anatomic illustrations. Some of the halftone reproductions could be replaced by simple line drawings. Moreover, text and illustrations should be integrated much more closely by a system of references. Printing and illustrations are good. C. F. L.

Neurosurgery—An Historical Sketch

Gilbert Horrax, M.D. American Lecture Series (Publication Number 117). 1952. Springfield, Illinois: Charles C Thomas, Publisher, 135 pages, $3.75.

This is a short account of the development of surgery of the nervous system from prehistoric to modern times. In the first half of the book a general review is given of cranial trephining up to the time of Horsley. Peripheral nerve and spinal cord surgery were considered by bold military surgeons but rarely practiced in these early times. The second half of the book records the modern era of brain surgery which stems from Victor Horsley, whom Horrax calls the father of neurologic surgery. This period, of which the author has had intimate knowledge, is described with many illustrations of its surgeons and their operative techniques.

There is a selected list of references but no index. The book has a pleasing format and is beautifully written. As a short sketch of the evolution of the specialty of neurosurgery, it should be welcomed by all who are interested in the nervous system. A. E. W.

A Textbook of Orthopedics

M. Beckett Howorth, M.D. 1952. Philadelphia and London: W. B. Saunders Company. 1110 pages, $16.00

Dr. Howorth and his associates have made a real contribution to the working library of the practicing neurologist as well as to that of the young orthopedist. This is not just a book of orthopedic technique but a well-organized and thoughtful study of the "diseases and abnormalities of the neuro-musculoskeletal system." In order to achieve this broad biologic basis Dr. Howorth has called in specialists to supply their own expert knowledge in the various fields of growth and development, neurologic disorders and the peripheral vascular diseases.

Of interest to the neurologist and neurosurgeon is the fact that there is an entire section devoted to neurology in orthopedics. This recognition of the importance of neurologic conditions and the need for an understanding of the basic anatomy and physiology of the nervous system is very gratifying. The book makes no pretense of being complete in the field of neurology and neurosurgery, but it will go a long way to bridge a gap so frequently seen in textbooks of the non-neurologic specialties. The principal value of the volume to the neurologist is the well-organized and easily available material on the congenital anomalies and developmental disorders which are so frequently seen by the practicing neurologist.

The section on poliomyelitis is well done and lays stress on the fact that "no form of treatment will result in recovery in the nerve cells which are destroyed, nor in the muscle bundles which they supply. Furthermore, regardless of treatment, spontaneous recovery will occur in the nerve cells which are only damaged, and in their muscles if they are given a chance. Treatment may aid this recovery but, most of all, should not interfere with or prevent recovery." The inclusion of poliomyelitis under the heading of orthopedic infections is unfortunate but does not vitiate the value of the section itself. The section on cerebral palsy suffers from the universal difficulty in defining this entity. The author states that while "mixed types" are occasionally found, usually cases will fit into either the spastic, athetoid or ataxic type. This is something of an over-simplification of the problem of classification of cerebral palsy. Two omissions are noted in the text material. Dr. Cramer, the author of the section on neurology in relationship to orthopedic practice, fails to mention the problem of compression of the median nerve at the transverse carpal ligament. This is an entity which one might expect to find in a textbook of orthopedics. In addition, there is no reference of platybasia. This entity has perhaps been overemphasized but certainly is worthy of note, particularly in relation to orthopedic practice.

More serious criticism can be leveled at the failure to discuss the possibility of the complications occurring with lumbar puncture and spinal fluid manometric studies. These are extremely valuable procedures, but they are techniques not without possibility of complication, and their value is limited in the hands of the inexperienced. Dr. Cramer has also seen fit to state that albuminocytologic dissociation is not a required condition for the diagnosis of the Guillain-Barré syndrome. Promulgation of this uncritical attitude can only lead to further confusion in classification of this and related disorders. Adherence to more rigid diagnostic criteria is to be desired.

These criticisms do not materially detract from the value of the book, which is an excellent contribution. The value to the neurologist is limited, but the section by Dr. McCune on developmental and growth abnormalities and other sections of the book on orthopedic problems as they relate to neurology are worthy of attention. A. L. D.

Precepts and Counsels on Scientific Investigation
Stimulants of the Spirit

S. Ramon y Cajal. Translated by J. M. Sanchez-Perez, M.D., edited and annotated by Cyril B. Courville, M.D. 1951. Mountain View, California: Pacific Press Publishing Co. 180 pages, $10.00.

"An organ of action intended for practical ends, our brain seems to have been constructed not to discover the ultimate reasons for things but to determine their immediate causes and their constant relations."

"I must declare that I find myself inclined to share De Maistre's opinion of the *Novum Organum* that, 'those who have made the most discoveries in science have not read it, and that Bacon himself did not arrive at a single discovery from his rules.' "

"These counsels are dedicated to the spirit more than to the intelligence, for I possess the conviction that the former, as Payot wisely affirms, is as capable of being educated as is the latter. I believe, moreover, that all superlative work, in art as in science, is the result of a great zeal pressed into the service of a great idea."

"Defect for defect, arrogance is preferable to diffidence; boldness measures its forces and conquers or is conquered, but excessive modesty flees from the battle and is condemned to shameful inactivity."

"In the chain of life all the links are equally valuable, for all prove to be equally necessary. We adjudge small what we see from afar or do not know how to evaluate."

"Let us cultivate science for its own sake, without considering its application for the moment. They always come; at times it requires years, at time centuries."

"Deficiencies of innate aptitude may be compensated for thorough persistent work and attention. It might be said that work substitutes for talent, or better yet that it creates talent."

"We may learn a great deal from books, but much more in the contemplation of Nature, the reason and occasion for all books. The direct examination of phenomena has an indescribably disturbing and leavening effect on our mental inertia, a certain exciting and revivifying quality altogether absent or scarcely perceptible in even the most faithful copies and descriptions of reality."

These are a few random quotations from a great treatise, an embodiment of the material used by Cajal on the occasion of his appointment to the Royal Academy of Medicine in 1893. The text scintillates in every paragraph, so much so that the brilliance might beguile the reader to stray from the thread of the thought. The volume is a product of Cajal's personal reflections, in which are skillfully interwoven the thoughts of many great scientists of the past. Even the kind of wife a scientist should have is discussed in detail. Novitiates as well as those long in the field of science are bound to pause to scrutinize their own endeavors as they read it. That the translation is a masterly one is evident in the quotations cited. W. H.

The Thalamus of the Macaca Mulatta
An Atlas for Use with the Stereotaxic Instrument

Jerzy Olszewski. Basel and New York: S. Karger. 36 pages of text with 57 plates, $18.70.

The objective of this atlas it to provide an anatomical guide for investigators who use the stereotaxic instrument for experimental physiological and anatomical studies on monkeys.

The material on which the atlas was based consisted of 20 brain of macaca mulatta monkeys. Model 4 of the Petrie

stereotaxic instrument was employed for placement of markers. Craniocerebral relationships were controlled by x-ray studies. The cerebra were meticulously fixed. The blocks of thalami were cut in serial sections in frontal, sagittal and horizontal planes. Ten specimens were cut frozen; six specimens were embedded in paraffin; four specimens were embedded in celloidin. The sections were stained with Nissl's method for nerve cells and Heidenhain's method for myelin. One specimen, embedded in paraffin and cut in the frontal plane at 24 micra, was selected as the basis for all measurements and photomicrographs reproduced in the plates at a standard linear magnification of x 18.

The atlas comprises 57 plates. The first five are diagrammatic drawings of the main structures of the brain stem and basal ganglia made by direct projection of the sections of another specimen and corrected under microscopic examination of the sections. These plates serve the purpose of general anatomical orientation in the frontal plane of section. The following 40 plates give the cytoarchitectonic and myelo-architectonic details of the thalamus in the frontal plane. The stereotaxic coordinates are indicated along the margins of each plate. These plates also contain 56 high-power microphotographs illustrating the cell type and the distribution patterns of cells in each nucleus. The last 11 plates are the outlines of the thalamic nuclei with the stereotaxic coordinates similarly indicated on the margins. These plates are intended for use as ready diagrams for the topographic recording of the experiments.

The atlas is provided with text describing the cyto- and myelo-architecture of each nucleus. The nomenclature of thalamic nuclei is based on that of A. E. Walker. The author carefully adheres to the long-needed uniformity and order in naming the nuclear complexes, the component nuclei of each complex, and the subdivisions of these componets. The nomenclature is in Latin. When the author needed a more detailed subdivision of nuclei than that already existing, he used the word *Pars* for the subdivisions of these nuclei which have more or less established connections. Several nuclei of the thalamus in the author's description receive a new and interesting treatment.

The first pages of the text are devoted to the description of the material and methods used in preparation of the book. Here a painstaking analysis is given of the factors which affect the calculations and require corrections for shrinkage and distortion of the cerebral tissue in the processes of dehydration, embedding and sectioning of the block. Orocaudal shrinkage in the direction perpendicular to the movement of the block on the microtome ways was found to be of little importance, whatever technique was used, but the shrinkage in lateral and dorsoventral directions was an important factor to be considered in calculations. The actual position of the thalamic structures shown in the plates was determined and corrected for the variable length of the macaque skulls. Here the aid of the x-ray film record of the position of the needles of the stereotaxic instrument in relation to the cranial landmarks, such as orbital ridges, internal auditory meati, and interior clinoid processes was essential. The results of the calculations are diagrammed and tabulated.

This atlas is a superb contribution to the descriptive anatomy of the thalamus and is destined to become an indispensable tool in the hands of all neurophysiologists whose experimental work requires an accurate stereotaxic placement of lesions and of the stimulating and recording electrodes in the thalamus of monkeys. The reproduction of the microphotographs in the plates is of unsurpassed excellence. The general format of the atlas and the arrangement of its contents are most judiciously chosen. The author and the publishers may be justly proud of this important publication. The Neurological Institute of Montreal, where this work was done, must be equally congratulated. P. I. Y.

Current Therapy—1952

Edited by Howard F. Conn. 1952. Philadelphia: W. B. Saunders Company. 849 pages. $11.00.

This large book of 849 pages attempts to cover in concise manner symptomatic and specific treatment of all diseases, disorders and syndromes. The editor has been assisted by an illustrious group of consultants and contributors. Diseases have been grouped under the usual categories found in textbooks of medicine.

Minor inconsistencies were found in the classifying of diseases. Poliomyelitis, an infectious disease of the nervous system, was treated under infectious diseases, whereas encephalitis, another virus infection of the nervous system, was treated under diseases of the nervous system. Some disorders were omitted.

The reviewer was unable to find out how tuberculous meningitis was currently being treated, for search under meningitis in the section of infectious diseases and under the section of pulmonary diseases where treatment of tuberculosis is covered failed to find tuberculous meningitis listed. Benign lymphocytic choriomeningitis failed to receive notice, as did Guillain-Barre Syndrome, a special form of polyneuritis, in the section on diseases of the nervous ssytem.

Reviewing this book confirms an impression of a deplorable widespread use of antibiotics as a non-specific treatment for a host of infectious diseases. Often the writer admits the controversial nature of the use of an antibiotic for the diseases in question and then goes on to list the current agents with dosage and method of administration. Such nonspecific and indiscriminate use of antibiotics frequently serves to uncover and render pathogenic, organisms that are otherwise held in check and prevents the development of natural immunity which is the logical barrier against infection.

Any reviewer could find cause for disagreement with some authors in a volume of such tremendous coverage, but it is hard to overlook Firor's admonition in his article on tetanus "at the time of the initial intravenous infectious it is important to give an intrathecal injection of 15,000 units of antitetanic serum." He indicates that this is a dangerous form of treatment. Not only does it seem dangerous, but entirely unphysiologic for Abel and Firor have demonstrated the irreversibility of toxin fixed in nervous tissue. The reviewer would add that the reaction between antitoxin and toxin must take place in the blood stream within nerve tissue not in the spinal fluid. The same criticism is made of authors writing on meningitis who recommend intrathecal injections of antibiotics. Almost any foreign agent injected into the subarachnoid space is a meningeal irritant—the antibiotics highly so—but to act upon the causative infective agent the antibiotic must be absorbed from the spinal fluid into the blood stream to be active within the brain parenchyma and within the meninges. Moreover, it can never reach the ventricles from the subarachnoid space.

These comments represent only a very small cross-section in the sampling of this book. The book is not for specialists but for the practitioner who must be prepared to treat everything that comes to him in his practice. He cannot be expected to have at his fingertips suitable treatment for everything. Such a reference as this should be a great boon to the general practitioner. Diseases of the nervous system in which the reviewer is especially familiar is well covered. The specialist in any field will find it a help in covering aspects of the patient's illness outside of his particular specialty.

M. G. M.

Neurology

The Essential Mechanism in Myotonia

An Electromyographic Study

William M. Landau, M.D.

THE prolonged muscle contractions which characterize the myotonic syndrome have been subjected to numerous investigations, the conclusions of which have differed, even since the development of refined techniques for recording the electrical activity of muscle.

Schaffer[1] and Adie and Greenfield[2] reported the absence of potentials during myotonic contraction, while Gildemeister[3] and Gregor and Schilder[4] found electrical activity. Ravin[5] has reviewed these studies and others which agree with both views. All of these workers used surface electrodes and, by present standards, relatively insensitive amplifying and recording systems.

Lindsley and Curnen,[6] using needle electrodes and recording system of low inertia, reported persistent activity during the myotonic contraction which they believed to be of central origin. They postulated hypersensitive muscle sense organs as the basic etiologic factor. Lefebre et al.[7] concluded from the "spontaneous" showers of activity in myotonic muscle that the myotonic muscle fiber is characterized by its "Aptitude à pulser." Buchthal and Clemmesen[8] demonstrated persistent myotonic electrical activity after brachial plexus block and found that local procaine abolished it. They believed that the defect lies in a muscular portion of the endplate region. Harvey,[9] on the basis of pharmacologic antagonisms, concluded that a defect in neuromuscular conduction exists in myotonia.

From the laboratory of neurophysiology, department of neuropsychiatry, Washington University School of Medicine, St. Louis, Missouri.

Work supported in part by fellowship grant from the National Paraplegic Foundation.

Other studies which excluded central nervous system activity were those of Grund[10] and of Kennedy and Wolf,[11] both of which demonstrated persistent peripheral myotonic reactions after spinal anesthesia. Schaffer[1] showed persistent myotonia after intramuscular procaine and nerve block, and Lanari,[12] after curarization.

The most detailed study in the literature is that of Denny-Brown and Nevin[13] who demonstrated persistence of "peripheral myotonia" after block of the ulnar nerve. They also described an innervated contraction in the forearm following grasp which they aptly called "after-spasm." They concluded that there is a central reflex disorder in myotonia in addition to the repetitive fiber activity peripherally.

The present work was initiated with the idea that such a primarily central pathologic mechanism might be responsible for the development of the entire clinical syndrome. It would have been necessary therefore to discount as a disease of another species the careful study of Brown and Harvey[14] on congenital myotonia in the goat. However, our experimental results in man and our conclusions agree with theirs in remarkable detail. It appears that all of the abnormal function in man is adequately explained by the hyperirritable muscle fibers themselves without reference to a special endplate abnormality or a reflex abnormality.

CASE MATERIAL

Six cases of myotonia dystrophica have been used in this study.* Maas and Patersen[15] have demonstrated on clinical grounds that there is no uniform distinction between myotonia congenita and late appearing syndromes. Electromyographic studies have also shown no qualitative differences.[6,8,13]

The majority of the observations were made upon one patient who submitted to weekly examinations over an eight month period. He was 30 years old and had had symptoms of muscular stiffness for four or five years. He was generally well developed muscularly. Atrophy was confined to the thumb web in the left hand (he was left handed) and there was moderate weakness of the foot extensors. Most of the examinations were done on the right upper extremity.

The prolonged study of one case has proved particularly advantageous in this investigation. This patient became as skilled as any of the normal laboratory subjects at accurately controlling individual muscle groups, both with and without reference to the activity being recorded on the oscilloscope or inkwriter. All of the general observations upon this patient have been confirmed upon the other patients studied. The other cases had varying degrees of upper extremity weakness and atrophy and varied in age from 27 to 49.

METHODS

All examinations were performed on the upper extremity, usually with the

*The patients were studied through the cooperation of Drs. H. Rosenbaum, W. B. Mills, J. J. Gitt, A. K. Baur and J. L. O'Leary.

patient in a sitting position. The forearm was placed comfortably on a cushion, usually in a neutral position. Voluntary grasp was studied in particular detail. A 5 cm. diameter cylinder was placed in the patient's hand and he was instructed to relax completely until the signal, then to squeeze steadily. At the signal to relax he was trained to relax the willed grasp without extending the fingers away from the cylinder.

Double core grounded shaft needle electrodes, consisting of two No. 40 (75 mu) Nichrome wires 20 to 400 mu apart in a No. 25 hypodermic needle, were used for all local recording. Such electrodes lead from a smaller area than ordinary concentric needles[16] and are particularly useful for recording during electrical stimulation.[17] Satisfactory fixation was secured by supporting the needle hilt with cotton pledgets and adhesive tape. For surface recording, copper wires were attached to the skin about 1 cm. apart with a wet paste made of two parts modeling clay to one part plaster of Paris. Most muscles of the forearm and hand were studied with both types of electrodes simultaneously and separately. For localizing activity in subcutaneous muscles and for quantitative evaluation of duration and degree of activity the surface leads proved quite as reliable as the needle leads.

Percutaneous nerve stimulation was carried out with brief condenser shocks using 1 cm. copper discs applied to the proper area with electrode jelly and adhesive tape. For muscle polarization 2 cm. saline pad electrodes were used, usually applied over the ends of flexor pollicis brevis. A Wagner ground in the stimulating circuit helped to reduce the shock artifact.

Activity was amplified with a push-pull amplifier and recorded with an inkwriting electroencephalograph, with a single beam cathode ray oscilloscope and bromide paper, and with a double beam cathode ray oscilloscope and 35 mm. film. The amplifier characteristic may be judged in the photographic records from the square wave time signal applied at one second intervals ahead of the filters.

RESULTS

1. *Peripheral myotonia*

Peripheral myotonia is by definition that sustained activity which can be seen after separation of muscle from the central nervous system. Confirming many workers we have found that myotonic phenomena persist after procaine block of the motor nerve. The ulnar nerve was blocked above the elbow in one patient, and the median, also above the elbow, in two.

"Spontaneous" activity in myotonic muscles independent of voluntary innervation has been seen by several observers who used needle electrodes.[7,8,13] The characteristic bursts (figure 1, A, B, C, E) are best seen in the more peripheral musculature where myotonia is more obvious clinically. Usually there is a gradual increase of frequency in a burst to a maximum rarely as high as 150 per second. There may be onset or cessation of activity at maximal frequency. Cessation, however, usually occurs after some slowing. Single potential discharges usually persist for a few seconds, although some have

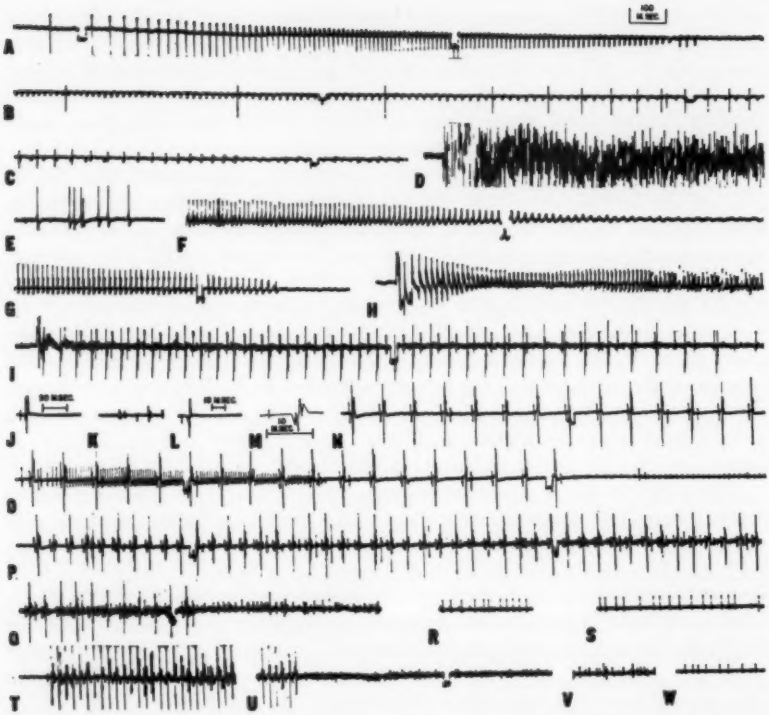


Fig. 1. Needle electrodes. A, Flexor digitorum sublimis. "Spontaneous" shower one second after relaxation of wrist flexion. B and C, Continuous record. Flexor digitorum sublimis. Low frequency shower starting 6 seconds after relaxation of grasp. D, Flexor pollicis brevis. Percussion myotonia, multi-fiber response. E, Flexor pollicis brevis. Unusual brief "spontaneous" shower of irregular potentials. F, Flexor pollicis brevis. End of response to percussion. Note the continuous diminution of spike amplitude with relative maintenance of amplitude of the slower potential change. G, Flexor digitorum sublimis. End of response to percussion 2 seconds after blow. Note the synchronized but distinct double spikes. H, Flexor digiti quinti brevis. Percussion. Two spikes are at first perfectly synchronized and then gradually separate. A square wave time signal occurs at the moment of the blow. I, Flexor pollicis brevis. Percussion after quinine. Note the triply inflected repetitive spike pattern. J, Flexor digiti quinti brevis. Response to single ulnar nerve shock. K, Same locus and amplification as J and N through W. Voluntary motor unit activity. Response to nerve stimulation consists of several synchronized motor units. L and M, Flexor carpi ulnaris. Response to ulnar nerve shocks at different sweep speeds. N through W, Flexor digiti quinti brevis. Ulnar nerve stimulation. N and O, Continuous record, 12 shocks/sec. Note the development of a high frequency fiber discharge in O. The variable form of the direct response to nerve stimulation is particularly evident at higher frequencies and is seen to a similar degree in normals. P, Q. Continuous record. 23 shocks/sec. Note the more rapid build-up of myotonic background activity. R, 5 seconds after last shock in Q. S, 9 seconds after last shock in Q. T, Beginning of stimulation at 58 shocks/sec. U, End of stimulation in T. V, 3 seconds after last shock in U. W, 9 seconds after last shock in U. Time for J and K in J. 10 msec. time line in L and in M. Time for all others in A. Square waves in this and subsequent figures are time signals.

been followed for as long as 20 to 30 seconds. This activity may be associated with needle movement,[13] but it is seen at times when electrode and muscle have not been moved for several minutes. To be sure, the bursts develop most commonly during the period immediately after strong voluntary contractions (figure 3, B, C, D) and are qualitatively indistinguishable from the myotonic potentials that appear during voluntary (motor unit) activity (figure 2,

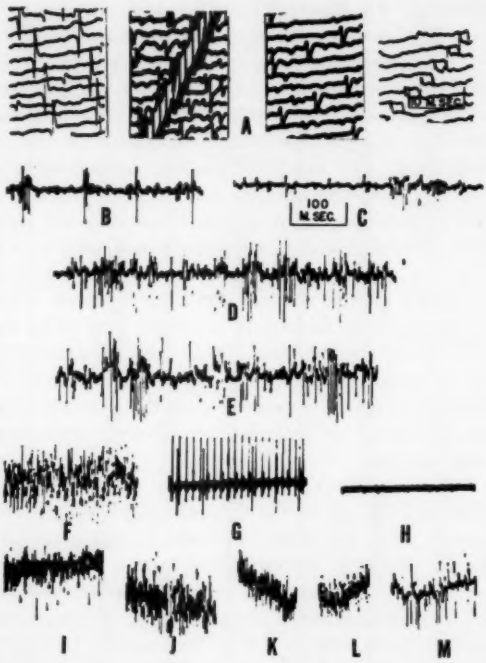


Fig. 2. Needle electrodes. Flexor pollicis brevis. A, Myotonic spikes at high sweep speed after direct current stimulation. Records were made using continuous transverse sweeps with paper transport speed the same as in the conventional records. The baseline is oblique. B through E, Flexor digiti quinti brevis. Abortive myotonic activity in association with varying degree of voluntary motor activity. Note the trains of high frequency spikes in association with and sometimes separate from higher voltage motor units. F, Flexor pollicis brevis. Response to percussion after curarization. G and H, Flexor pollicis brevis. Activity 4 seconds after make of direct current before and after administration of 0.5 gm. quinine hydrochloride intravenously. Locus, current intensity and amplification are the same. Electrical and mechanical myotonia were not completely abolished. See Fig. 1, I. I and J, Flexor pollicis brevis 6 seconds and 3 seconds respectively after make of the same direct current, before and after administration of 20 cc. of 10 per cent calcium gluconate intravenously. K and L, Flexor pollicis brevis. 4 seconds after make of the same direct current, before and after intramuscular administration of 1.5 mg. of prostigmine. M, Flexor pollicis brevis, same patient as K. Activity 7 seconds after make of same direct current as in K, sixth day of Cortisone administration. 10 msec. time line in last strip of A. Time for other records in C.

B–E) (figure 3, O–Q), or activity induced by nerve stimulation (figure 1, 0). Since myotonic muscle is characterized particularly by its mechanical irritability, and since it is impossible to control the local traumatic effect of needle electrode insertion, one cannot be certain using local leading whether any activity is really "spontaneous". On several occasions, however, bursts of such activity have been recorded with surface leads (figure 4, B and E).

The myotonic response to percussion (figure 1, D, F, G, H, I) or to any mechanical stimulation is qualitatively similar to the spontaneous activity, except that the frequency immediately following stimulation is usually the highest obtained. A higher range of frequencies is usually seen after percussion than occurs spontaneously. The nature of myotonic activity in a few fibers can be most readily demonstrated by percussion (figure 1, F, G, H, I), although multifiber responses (figure 1, D) may also be seen. With the needle apparently fixed in position and with constant percussion technique, response to percussion is quite variable. Not only is there a great deal of variation in amplitude and duration of responses, but often there is no response at all. Response of the same units in successive percussions has not been identified, partly, no doubt, because the electrode is not maintained in the same relative

position. An apparent fatigue is seen with repeated stimulation, but this cannot be definitely distinguished from local injury by the rigid electrode.

The prolonged response to threshold direct current stimulation (myotonic reaction) is evidently (figure 3, T-Z) a relatively asynchronous summation of "spontaneous" myotonic showers. With near threshold currents recruitment of fibers as well as increased frequency of discharge can be seen during polarization. The myotonic reaction is seen at or slightly below threshold for "twitch" response at make and break of stimulating current. Reversal of end to end polarizing current in a muscle does not significantly affect the threshold for myotonic response; since the motor point does not have a lower threshold,[18] a neural mechanism is apparently not concerned. After the break of polarizing current a gradual diminution of the myotonic activity is seen (figure 3, T, U). With adequate fixation of electrode and limb, the myotonic reaction can be reproduced on repeated trials with considerable accuracy. Frequently the same initial potential, if of sufficient amplitude, can be seen with each stimulation. Current threshold remains constant over long periods of time. A small amount of fatigue may be seen with rapidly repeated or prolonged polarization.

The usual spikes of myotonic activity recorded with needle electrodes (figure 2 A) are of the duration and amplitude of fibrillation discharges recorded with the same electrodes.[17] Potentials of longer duration (figure 1, E, F) probably represent synchronized activity to some extent even when separate spikes cannot be clearly demonstrated as they are in figure 1, G, H, I.) Synchronization is obvious where myotonic activity is recorded with gross surface leads (figure 4 B). Presumably the mechanism of such mutual discharge consists of action potential stimulation of neighboring fibers. Although the possibility must be considered that antidromically excited nerve fibers are involved in synchronization,[19] such a theory is not necessary, for synchronized discharges of similar nature have been recorded from denervated muscle.[17,20]

Indeed, the resemblance is striking between myotonic discharges and both the responses of amphibian muscle to injury[21] and the activity of denervated mammalian muscle.[17]

Changes in amplitude during the course of a myotonic shower are fre-

Fig. 3. A, B, C and D, Continuous record. Flexor digitorum sublimis, needle electrode. Patient ordered to squeeze and relax grasp at signals (produced by grounding input through capacity). Note that the activity after relaxation is characteristic of "spontaneous" myotonic showers rather than of motor units. Activity persisted for 4 seconds after end of D. E and F, Flexor digitorum sublimis, surface leads. Resting record in E. End of grasp at signal in F. G, Flexor carpi ulnaris, needle electrode. At signal, end of grasp during which this locus was not active. H, 3 seconds after G. I, 5 seconds after H. Note that the potentials represent motor units. G, H, I, L, O, P and Q are taken with the same electrode and amplification. J and K, Flexor carpi ulnaris, surface leads. Resting record in J. End of grasp at signal in K. Compare the higher voltage synchronized activity of innervated contraction with the myotonic activity in F. M and N are taken with the same electrodes and amplification as J and K. L, Flexor carpi ulnaris, needle electrodes. Relaxation of moderate strength wrist flexion at signal. There is no evidence of peripheral myotonia or of after-spasm. M and N, Flexor carpi ulnaris, surface leads. Relaxation at signals respectively of wrist flexion and of ulnar wrist flexion. O, Flexor carpi ulnaris, needle electrode. Strong wrist flexion and relaxation at signals. Note buildup of myotonia. Compare with L and with Fig. 1, O. P, 1 second after O. Q, 2 seconds after P. R, Flexor pollicis brevis, needle electrode. Order to relax flexion at signal. Note envelope of residual myotonic activity. S, Flexor digiti quinti brevis, needle electrode. End of ulnar nerve tetanus at 58 shocks/sec. Note rebound innervated contraction superposed on myotonic remainder. T and U, Continuous record, flexor pollicis brevis, needle electrode. Direct current stimulation, make and break at signals. Note increments of frequency and of number of active units during current flow. V, Flexor pollicis brevis, needle electrode, resting record. W, .5 sec. after make of direct current, same locus as V. X, 2 seconds after make. Y, 4 seconds after make. Z, 6 seconds after make.

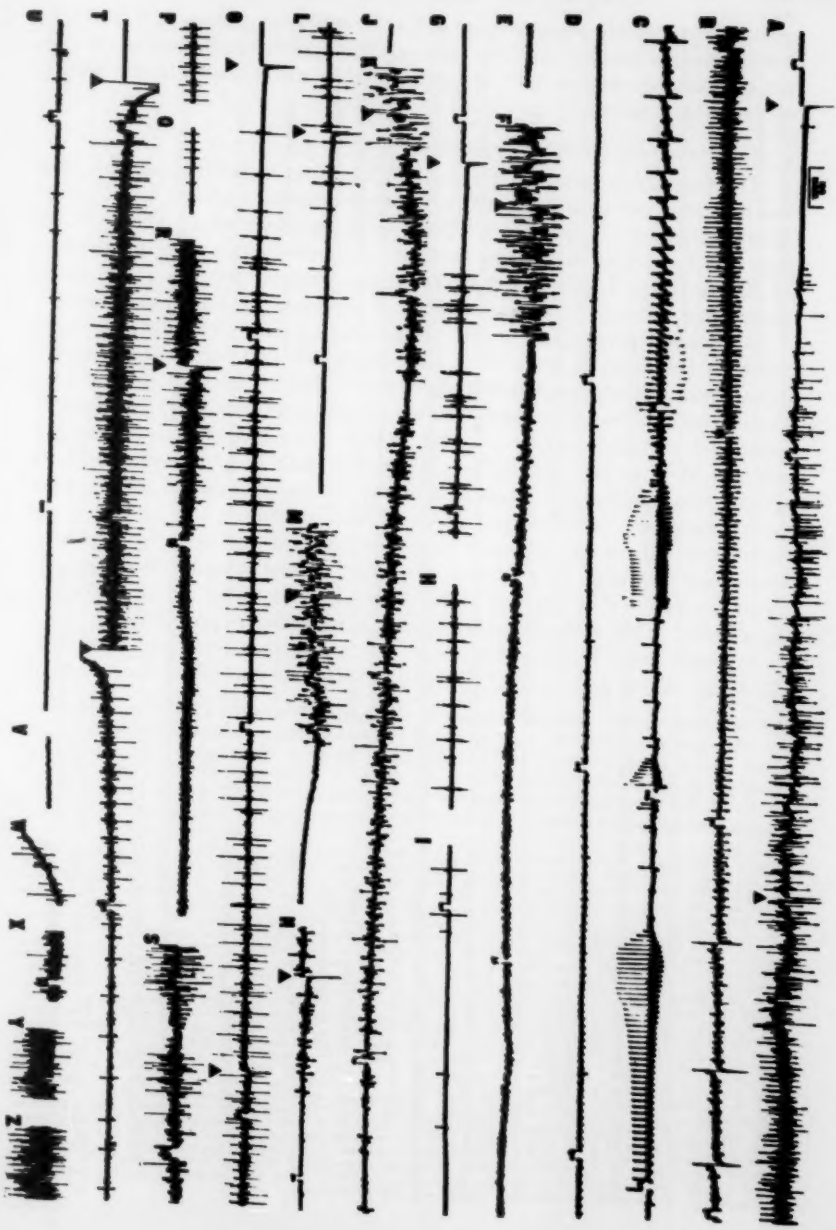


FIGURE 3.

quently seen. Decremental change is usually observed (figure 1, A, B, C, F) but continuous increase may also be seen (figure 3C). Needle movement does not satisfactorily explain such changes, for they are not seen in the activity of denervated muscle.[17]

2. *Neuromuscular excitation in myotonia*

The majority of motor unit activity in myotonia is indistinguishable from the repetitive polyphasic potentials of normal muscle (figure 3, A, G, O).[13] Minor variations of potential form are sometimes seen as in normals,[22] but they may be attributed to slight electrode movement rather than to alteration of fiber activity. Lambert and Beckett have reported that the amplitude of motor units falls off during the buildup of myotonia, with later recovery.[23]

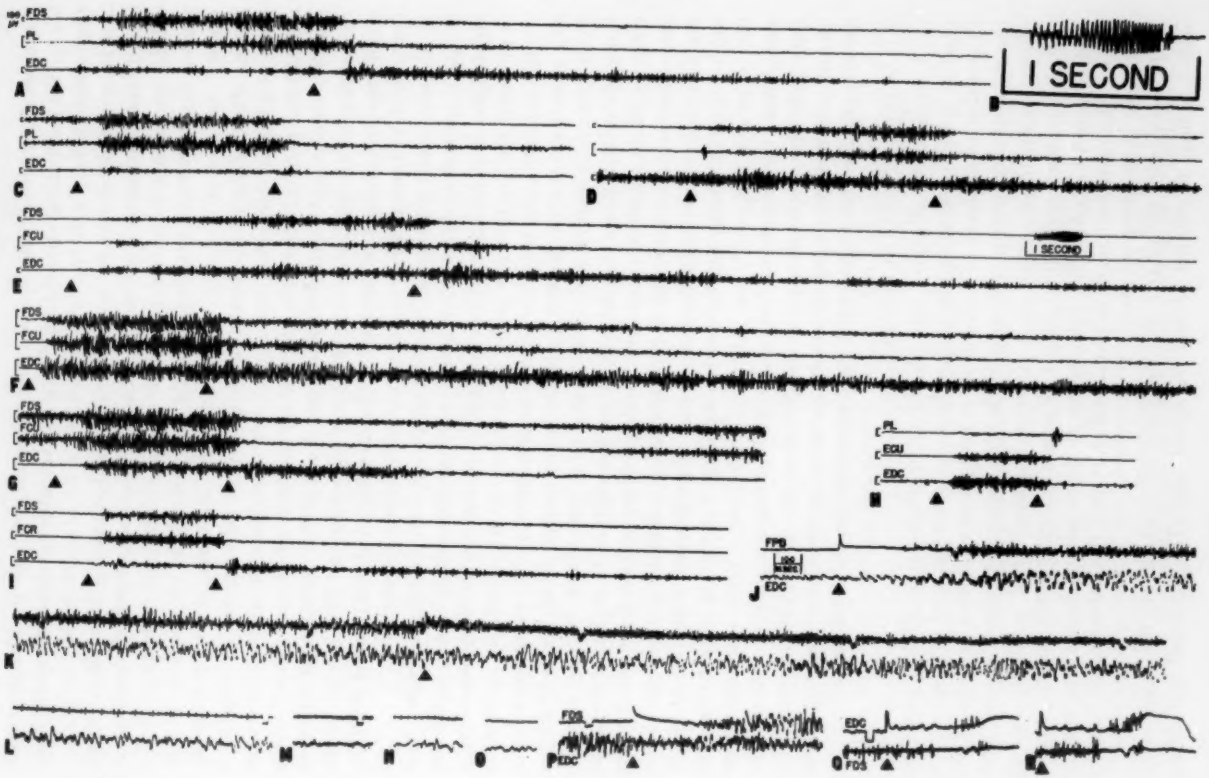
Sometimes, particularly in the distal musculature, short high-frequency bursts of fiber activity are seen in association with and occasionally separate from obvious* motor unit potentials (figure 2, B-E). These bursts are more evident with increased voluntary activation, and evidently eventually become prolonged enough to outlast voluntary activity for a considerable period (figure 3, A, B, C, D, R). It is to be expected that since fibers active in myotonic discharge are presumably innervated, mutual interference should be seen when both neural and "spontaneous" forms of fiber excitation are present at the same time. However, on many occasions attempts to produce change in motor unit discharge by percussion or direct current stimulation during voluntary activity, or to "pick up" a myotonically active fiber into a motor unit have failed. That such phenomena occur is nevertheless probable.

A single shock to the motor nerve does not produce any consistent after-discharge (figure 1, J, L, M).[13,24] Occasional bursts that follow single stimuli

*Motor unit potentials frequently cannot be distinguished from the activity of single fibers or other groups of fibers by their form and amplitude alone, particularly with the highly local leading of our electrodes. When the active myotonic fibers are not present in large numbers at the needle tip (figure 3, R, S), or when larger areas are led from (figure 3, F, K, M, N) the distinction is more obvious. A distinction based upon frequency of discharge and relation to intensity of voluntary innervation is usually satisfactory.

Fig. 4. A through I, Surface leads, inkwriter records, FDS=flexor digitorum sublimis, PL= palmaris longus, EDC=extensor digitorum communis, FCU=flexor carpi ulnaris, ECU=extensor carpi ulnaris, FCR=flexor carpi radialis, FPB=Flexor pollicis brevis. A, Wrist flexed 20°. Squeeze and relax grasp at signals. Note that the most prominent after-spasm is in EDC. Its activity is reflected at lesser amplitude in PL. Slight low amplitude activity is seen in FDS. B, Enlarged illustration of myotonic shower in E. Spike form is, of course, distorted by mechanical recording system. Compare with Fig. 1, A and B. The patient became aware of the burst when he heard the unexpected buzz of the inkwriter, and was then able to indicate the muscle which had "twitched." This was the only occasion of any subjective awareness of single showers. C, Same as A with wrist flexed 90°. D, Same as A with wrist extended 25°. The longest duration of after-spasm is seen with the wrist within 10° to 20° of the straight position. E, Wrist flexed 20°. Squeeze and relax grasp at signals. The pattern of activity in FCU is not significantly different from that in PL. Note the "spontaneous" myotonic shower in FDS (also in B). F, Wrist straight. Squeeze and relax grasp at signals. At higher amplification sustained low voltage activity is more clearly seen in FDS. The degree of activity in FDS is reflected in EDC. G, Wrist flexed 80°. Squeeze and relax grasp at signals. There is a brief after-spasm in EDC in this posture. As it relaxes there is reciprocal postural contraction of FDS and FCU. H, Extension of wrist and relaxation at signals. Note large burst in PL followed by shorter reciprocal burst in EDC. Compare with A, and Q, R. I, Flexion of wrist very strongly and relaxation at signals. Note sustained after-spasm burst in EDC. J through R, Two beam oscilloscope. J through O, Needle electrode in FPB, surface leads on EDC. J and K are continuous. Squeeze at signal in J and relax grasp at signal in K. L is taken 7 seconds after K; M, N and O successively at 3 second intervals. Note the reflection of myotonic discharge in FPB in EDC. P, Surface leads. Squeeze at signal. The after-spasm from preceding grasp in EDC is diminished somewhat as innervated activity begins in FDS and a new posture is assumed. Q and R, Normal subject, needle electrodes. Relax grasp at signal. There was little EDC activity during grasp in the posture assumed. Note the reciprocating bursts in both muscles. The burst in FDS is seen less commonly than the typical response in EDC. Time for inkwriter in E; for oscilloscope records in J. Calibrations for inkwriter records are 100 microvolts.

FIGURE 4.


FDS
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do occur more often than "spontaneous" showers, but are readily accounted for by the mechanical stimulation that is unavoidable using rigid needle electrodes in twitching muscle.

Using double shocks to the ulnar nerve and recording from flexor digiti quinti brevis, attempts were made to find if there is any optimal shock interval for producing consistent repetitive discharge. In one experiment it appeared that repetitive discharge usually followed shocks at intervals of 3 to 4 msec., but not at longer or shorter intervals. However, the repetitive discharge often began at an interval after the direct response which suggests a reflex discharge. Moreover, the experiment was repeated on four occasions on the same patient, once after procaine nerve block, and in one other patient, and the results could not be reproduced. Even with two maximal tolerated nerve shocks, no consistent after-discharge is produced. The results in the single experiment must be ascribed to the mechanical stimulation of the electrode produced most effectively at a particular shock interval.

Tetanic nerve stimulation at various frequencies (figure 1, N-W) produces a gradual buildup of myotonic background activity, more rapidly at higher rates of stimulation. These potentials are not constant from one tetanus to the next; the myotonically active fibers appear to be selected at random.

There is some variation in form and amplitude of the summated motor unit response to nerve shock stimulation, more marked at higher frequencies. It is random in nature and little if any more prominent than in normals. It may be related to varying degrees of synchronization, to slight needle movement, to slight variations in shock duration, or to occasional failure of nerve fiber response to percutaneous stimulation, where reliable supramaximal shocks are difficult to obtain in the human subject. A progressive falling off of amplitude of direct response during the development of myotonia, with recovery as the myotonia fatigues,[23] has never been observed. With sustained nerve stimulation, fatigue of myotonic activity does become very prominent, and sometimes the myotonia may be abolished so far as the electromyographic record is concerned. Again the injurious effect of repetitive pounding of the irritable muscle fibers against the rigid electrode may be significant.

3. *The effect of drugs in myotonia*

A satisfactory objective test of muscle excitability in clinical myotonia must be reliably reproducible, subject to minimal fatigue, and as insusceptible as possible to artifacts of movement, posture, and voluntary activity. From the data already presented it appears that the response to direct current stimulation meets these criteria best. Clinical examination of voluntary activity and of percussion and direct current responses generally confirmed the results. The response to end-to-end polarization of flexor pollicis brevis was used as a test. The most prominent technical difficulty was the balancing of stimulus and tissue polarization artifacts.

In one patient the muscle was curarized by injection into the radial artery with a venous tourniquet around the upper arm. The threshold and degree

of response to direct current and to percussion (figure 2 F) were unchanged, confirming Lanari[12] and Jasper.[29]

Quinine hydrochloride (0.5 Gm.) intravenously produced significant depression of response (figure 2, G, H), although a fatiguable response persisted with larger currents, and a significant response to percussion could still be elicited (figure 1 I). Clinically the myotonia was improved to the extent that the hand could be "loosened up" to a maximal degree by only one voluntary grasp.

Calcium gluconate (20 cc. of 10 per cent solution) intravenously produced no significant electromyographic change (figure 2, I, J). On the first occasion when it was used there was subjective improvement. However, the patient became considerably more critical after the quinine treatment, and subsequently did not claim any subjective change with calcium gluconate.

Prostigmine (1.5 mgm. with 0.6 mgm. atropine) intramuscularly produced neither a significant degree of change in direct current response (figure 2, K, L) nor an increase of "spontaneous" activity in two patients. A few involuntary twitching movements were produced in one patient.

Adrenalin, 0.4 mgm. intravenously, produced no significant change in one patient.

One patient was treated with intramuscular desoxycorticosterone acetate, a total of 95 mgm. being given over a 10 day period. He was kept on a diet containing less than 2 Gm. of KCl and about 5 Gm. of NaCl daily during the period of study. Serum potassium values* which normally ranged between 4.7 and 5.15 meq./L. dropped very little; the minimum value of 3.9 meq./L. was obtained on the eighth day, even though a dose of 30 mgm. of Doca was given on the ninth day. Weight and electrocardiographic tracings did not change significantly. There was no clinical or electromyographic change in the myotonia.

The same patient was treated with 1 Gm. of Cortisone over the course of a week. He received 300 mgm. the first day, 200 mgm. the second day, and 100 mgm. on each successive day. Adequate eosinophil responses were checked on the first and last days of therapy. No objective clinical or electromyographic improvement was observed** (figure 2 M). Although the euphoria which frequently occurs with Cortisone therapy[26] was quite evident in this patient, who stated that he felt like walking ten miles, actual strength and stiffness were unchanged. The apparent improvement seen by Shy et al. may be so explained.[27]

Confirming Buchthal and Clemmesen[8] it was found that local intramuscular injection of 1.0 per cent procaine abolished myotonic activity. However, the depression of repetitive myotonic activity was accompanied and followed by the complete silence of the area recorded from to any kind of stimulation.

*Through the cooperation of Dr. Theodore Weichselbaum the potassium determinations were done with a flame photometer each morning before the next dose was given.

**Since this paper was submitted for publication we have observed an additional failure with Cortisone and one with ACTH.

A similar depression of fibrillation in denervated muscle is readily demonstrated. That no specific depression is to be expected is evident from the established observations[28,29] that procaine abolishes propagation of potentials. In regard to the question of contracture in myotonia, it is of interest that no electrical or visible activity is seen with direct current stimulation after adequate muscle infiltration with 1.0 per cent procaine. The swelling produced by intramuscular isotonic saline diminished myotonic potentials to a small degree. The results with half isotonic and twice isotonic saline were not essentially different. A questionable increase in "spontaneous" activity was produced with 1.0 per cent potassium chloride.

4. *After-spasm in myotonia*

As Denny-Brown and Nevin pointed out,[13] there is a clinically evident renewed contraction in the forearm of myotonic patients following release of voluntary grasp. This activity was present to greater or less degree in all of our patients, more prominent in cases where strength was good and peripheral myotonia more marked. Since the essential involuntary nature of this renewed contraction was emphasized by these authors, a maximum degree of subjective relaxation and sophistication in control of activity was developed in the subjects of this study.

During grasp in myotonia, the predominant activity is in the long finger flexors and in the intrinsic hand muscles (figure 3, A, F, figure 4, A-G, J-O). Some synergic activity is seen in both finger and wrist extensors and to a less extent usually in the wrist flexors.[30] Following the command to relax grasp and following the relaxation of the prime movers by 50 to 500 msec., there is a sustained burst of activity in many of the forearm muscles, not apparently directly related to the degree of activity in those muscles during grasp. That this is predominantly innervated motor unit activity is readily demonstrated with needle electrodes (figure 3, G-I).

The relative specificity of the after-spasm phenomenon in the movement of grasp is shown in flexor carpi ulnaris (figure 3, G-K). With identical leads there is no central after discharge after wrist flexion or ulnar deviation (figure 3, L, M, N), although there may be peripheral myotonic activity after any strong movement (figure 3, O, P, Q). However, a strong movement of wrist flexion, which actually activates both finger and wrist flexors as in grasp, may be followed by sustained after-spasm in extensor digitorium communis (figure 4, I) and with strong movements of the forearm, a slight degree of after-discharge may be seen in the arm musculature.

Posture is quite important to the degree and duration of after-spasm in grasp. With the wrist 10° to 20° from the straight position maximal activity occurs (figure 4, A, E, F). With extreme flexion (figure 4, C) or extension (figure 4, D, G) it is greatly diminished. The most prominent and longest sustained contraction is seen in the finger and wrist extensors. Activity of similar pattern but of shorter duration is seen in the wrist flexors, particularly palmaris longus and flexor carpi ulnaris (figure 3, C-K, figure 4, A, E, F),

and to less extent in flexor carpi radialis. The variation of synergies with posture may be seen in figure 4 G, where the wrist flexion postural activity in flexor carpi ulnaris appears reciprocally with the disappearance of after-spasm in extensor digitorum communis. In figure 4 P some relaxation of after-spasm in extensor digitorum communis is seen during the development of a new grasp synergy which includes a lesser degree of activity in extensor digitorum communis than occurs during the after-spasm.

Voluntary relaxation of after-spasm can be obtained only to a limited degree by innervated wrist and finger flexion. Fatigue of after-spasm is seen to a moderate degree with repeated contractions, possibly developing a little earlier than apparent fatigue of peripheral myotonia. With strong enough muscular contraction and proper positioning, however, after-spasm is a relatively constant finding.

The peripheral myotonia following strong grasp is most prominent in the long and short finger flexors. Because of its generally asynchronous character it is rather poorly demonstrated with surface leads (figure 3 F, Figure 4, A-E) with occasional exceptions (figure 4 B). With the high amplification relative to the amplitude of innervated activity, peripheral myotonia may be demonstrated for longer intervals after grasp (figure 4 F). Needle electrodes in flexor digitorum sublimis may demonstrate peripheral myotonia after strong grasp for as long as 15 to 30 seconds (figure 3, A-D). Such responses, however, are not constantly seen with repeated grasp movements and the same electrode position. In flexor pollicis brevis after grasp a more consistent sustained myotonia is seen which may last over 30 seconds (figure 4, J-O), but exceptions are seen here also. Any theory of the mechanism of after-spasm and peripheral myotonia must explain the fact that the former usually outlasts the latter, rarely persisting as long as a minute or more. Since after-spasm is not seen in the absence of peripheral myotonia, a significant relationship may be presumed to exist.

Three possible explanations for after-spasm may be considered: (1) hyperexcitable muscle sense organs or excessive excitation of normal sense organs by the local peripheral repetitive contraction results in exaggerated reflex activity;[6] (2) central reflex abnormality results in involuntary activity following grasp;[13] (3) after-spasm is an exaggeration of normal reciprocal muscle activation attributable to the contraction of peripheral myotonia alone.

Grasp in the normal subject may well be described before considering these theories. The muscles active during grasp are the same as in the myotonic. Following the order to relax and following cessation of activity in flexor digitorum sublimis by about the same interval as does after-spasm, there is usually a short burst of activity in the finger and wrist extensors (figure 4, Q, R). Less commonly a "rebound" burst is seen in flexor digitorum sublimis. This involuntary phenomenon is readily demonstrated in movements in the myotonic that do not produce typical after-spasm. It has been seen with both surface and needle electrodes in palmaris longus and flexor carpi ulnaris fol-

lowing wrist extension (figure 4 H), in flexor carpi ulnaris following radial wrist movement, and reciprocally in adductor and abductor pollicis brevis.[13] After median or ulnar nerve block of different groups of flexor muscles in myotonia, with abolition of true after-spasm, a short burst similar to that in the normal is still seen in extensor digitorum communis after grasp. The rebound burst following tetanic artificial motor nerve stimulation in normals as well as myotonics (figure 3 S) is probably a related phenomenon. It appears then that at least the initial burst of myotonic after-spasm (figure 4, A, E) is an example of normal reciprocal innervation. Still to be explained are its prolongation and the activity in the wrist flexors, which are not usually active to this degree in normal grasp release.

If after-spasm were the result of abnormal afferent discharge from the prime movers, one might expect that it could be reproduced by stimulating the nerves to those muscles. As in normals, however, stimulation of median or ulnar nerve at frequencies up to 60 per second produces no activity in the resting extensor muscles. Intensities were used which produce maximal tolerated muscular contractions and must therefore stimulate muscle afferent fibers of the same size as the motor fibers. Since the strong muscle contraction might result in reflex inhibition, stimulation was carried out above nerve blocks, again with negative results. These results are also negative in relation to a central reflex abnormality. Because reflex excitability of the spinal cord is doubtless different at rest from that during and after grasp, repetitive median and ulnar nerve stimulation above a block was initiated just before or at the moment of relaxation of voluntary grasp. Although no after-spasm resulted, such negative results do not disprove these theories.

Other experiments gave more positive evidence. If an involuntary persistent contraction ("peripheral myotonia") be produced by tetanic median nerve stimulation in a normal subject just at the moment when the command to relax grasp is given, an exaggerated burst of activity appears in extensor digitorum communis that may last for several seconds. The same result is seen if the stimulation is carried out below a block of the median nerve in the normal or the myotonic subject. In one myotonic subject median nerve stimulation below the block was carried out during voluntary grasp. Following relaxation the rebound burst in extensor digitorum communis was prolonged about one second. Admittedly these experiments do not demonstrate an "artificial after-spasm" of the duration and degree seen in myotonic grasp. However, the normal relations of muscle synergy and joint position cannot be exactly duplicated; yet the qualitative results are distinct.

It appears that after-spasm is the result of a lengthening reaction or stretch reflex, primarily in the extensor muscles, produced by the sustained peripheral myotonic contraction of the flexors. In the intact subject a voluntary "set" for relaxation is essential in order for the unwonted stretch to elicit a response. Since this response is an integrated one depending upon the total tension of peripheral myotonic activity, and since peripheral myotonic activity is scat-

tered at random throughout the prime movers, it is to be expected that local leading will not always demonstrate peripheral myotonia lasting as long as after-spasm. For the latter reason also, surface leads are unsatisfactory for demonstrating the total duration of scattered asynchronous fiber activity.

The synergic activity of wrist flexors with the extensors has still to be explained, since it is not usually prominent in ordinary movements of finger extension. It was found in a normal subject during voluntary extension against artificially induced flexion due to median nerve stimulation that flexor carpi ulnaris entered into strong and sustained cocontraction. The synergic relations of muscles about the complicated joint system of the hand are equally complicated and wrist flexor synergy with finger extension is evidently best seen against a background of finger flexion.*

Since there may be considerable activity of the extensor muscles during grasp and therefore some degree of peripheral mytonia in them, it might be expected that some after-spasm should be evident in the finger flexors. Its absence in our records must be attributed to an increased tendency to myotonia in the flexor muscles and to their initial excitation by a much greater volume of innervated activity. Any tendency to after-spasm in the finger flexors is apparently overwhelmed by the after-spasm in the extensors.**

There does not seem to be any characteristic of the after-spasm phenomenon which necessitates explanation by an abnormal neurological mechanism nor is there any reason to believe that *per se* it produces any embarrassment of movement. Even though this recovery mechansim of innervated contraction may produce some more peripheral myotonia, the former in itself does limit the disability due to the sustained contraction of peripheral myotonia.

DISCUSSION

Since Denny-Brown and Nevin[13] considered and rejected the possibility that after-spasm is an effort of the patient (consciously or unconsciously) to overcome the impediment to relaxation of peripheral myotonia, their data may well be re-examined in relation to the present study. Since they used relatively less localizing needle electrodes, a slow camera speed, and a recording system that was not inertia free, a striking difference was seen between the "fluffed" activity of single fibers and the synchronized discharge of motor units. Since they apparently assumed that all synchronized potentials represent motor units, they may have drawn a different interpretation from some of the large potentials of peripheral myotonia in the prime movers of grasp.

Their subjects were frequently either instructed or allowed to *extend* the fingers after grasp; it is not surprising, therefore, that they should frequently have had rebound innervated contraction of the long finger flexors such as

*Beevor[30], concerning normal grasp release, wrote, "If they (the fingers) be quickly extended, the flexors of the wrist are felt to contract synergically, and if in this condition pressure be made against extension of the wrist . . . . the flexors of the wrist will not relax."

**It may be that the long finger flexor after-spasm seen by Denny-Brown and Nevin[13] does in part represent innervated response to extensor periphral myotonia (see discussion).

often occurs in normals (figure 4, Q, R). (In myotonic patients in this study such bursts were often seen if finger extension was allowed). An exaggerated peripheral myotonia from this intense synchronized innervated burst could then be misinterpreted as sustained after-spasm. Their own statement that such action currents may increase in frequency and size while the muscle belly relaxes is difficult to explain entirely as increased innervated activity, and suggests that the apparent exaggeration may be related both to peripheral myotonia produced by the innervated twitch itself and to that produced by local mechanical trauma by the needle during the twitch. A small degree of sustained innervated activity in the long flexors probably represents postural activity in the untrained subjects.

Denny-Brown and Nevin's observation that after-spasm in muscles other than the prime movers may surpass in quantity the activity during grasp agrees with our observations. The presumption that the predominant activity of the extensor muscles after grasp is willed relaxation and of an essentially different nature from after-spasm in other muscles is opposed by the results presented here.

After-spasm cannot be strictly classified in physiologic terms. It is a reflex in the sense that it is not strictly consciously willed activity, although it depends upon the voluntary "set" of the reciprocal spinal mechanism and may be varied but not abolished by voluntary activity. The relation to posture and the variable latency indicate that it is basically a stretch response or lengthening reaction. There is no reason to believe that it is in any sense a pathological reflex at central or peripheral sites in regard to abnormal neural response. It is rather a normal response to a sustained muscle fiber contraction which is independent of neural control. Any more elaborate theory must meet the objections that there is no pathological evidence for another mechanism and that the phenomenon varies in degree with the degree of peripheral myotonia as determined by degree of effort, by fatigue, by flexor motor nerve block, and by medicinal therapy (quinine).

The essential nature of peripheral myotonia is highly similar to that of denervated muscle (with an intact nervous excitation mechanism). The patterns of activity in myotonia may also be seen in denervated muscle, particularly with local tissue injury,[17] and general characteristics of "spontaneous" activity, increased mechanical and electrical excitability, "warming-up," pharmacologic responsiveness, and histologic change are common to both.[2,31,32] There is, however, no evidence to support a corollary conclusion that the "trophic" effect of the motor nerve is what is lacking in myotonia. Rather it appears that the phenomena of both conditions are characteristic of hyperexcitability in muscle.

Whether the hyperexcitability of the myotonic fiber resides primarily in the endplate region, or whether it is an overall characteristic cannot be certainly established without careful studies such as Kuffler has made with single fibers or small groups under direct observation. Buchthal and Clemmesen[8]

concluded that endplate excitability is responsible, using the unproven assumption that procaine affects the endplate selectively. Many workers[9,11,33] have stressed the antagonistic responses in myotonia and myasthenia gravis to quinine and prostigmine, and have concluded rather conveniently that the diseases involve the endplate mechanism in opposing manners. Harvey[9] admitted that such evidence is not at all conclusive, and has shown other significant quinine effects besides a curariform one.[34]

It would appear likely by comparison with denervated muscle that there be proportionate increased excitability of the endplate region as well as of the rest of the fiber.[32] The only available evidence in myotonia derived from pharmacologic investigation of whole muscles, does not demonstrate any critical variation from normal.[11,33,35,36] This study confirms the results of Ravin[37] that there is no lowering of threshold to prostigmine in myotonia. Lanari[35] reported a lowered threshold to intra-arterial acetylcholine in myotonia, but also noted that the dose which purportedly produced no response in normals did cause contraction in several diseases of the central nervous system. The result appears even less convincing when the diminished muscle mass in myotonia is considered in relation to the dose. In myotonia in the goat there is also no eserine or acetylcholine hypersensitivity.[14] It is difficult to believe that the characteristic gross responses to percussion and direct currents in myotonia are entirely the result of stimulation of endplate alone.

The characteristic amplitude variations in myotonic potentials are seen too often to attribute them to electrode movement, although it may be that contraction of an active muscle bundle causes a relative change in electrode orientation. Many of the changes are doubtless related to slight temporal variation in degree of synchronization of fiber activity (figure 1, G, H), and may also be seen rarely in denervated muscle.[17] The dropping out of fibers in synchronized activity no doubt occurs, but a discontinuous amplitude change that might be expected has not been seen. The progressive diminution of spike amplitude in records such as figure 1 F is highly similar to the change in veratrinized muscle preparations where a concomitant slow potential can be demonstrated as the fiber goes into contracture.[29,38] The occasional progression of isolated fibers or fiber groups into contracture would not controvert the accumulated evidence that the majority of myotonic tension is produced by propagated contractions. Brown and Harvey have discussed the similarity of behavior between myotonic and veratrinized muscle.[14]

Whether the fibers that become "spontaneously" active in voluntary activation of myotonic muscle are included with or may be merely contiguous to the muscle fibers of active motor units is not known. It appears likely that both phenomena occur (figure 2, B-E), excitation by neighboring muscle fiber action potentials as well as by a neural mechanism. Neighborhood effects of movement per se and of metabolites may be involved also.

Lambert and Beckett have recently shown, using integrating surface leads and repetitive nerve stimulation (optimum, 5/second), that over the course

of seconds there is a progressive diminution in the size of the response potential of myotonic muscle, with subsequent recovery.[23] Apparently the "spontaneously" active fibers are refractory to neural excitation. Lambert and Beckett have claimed that similar changes are seen with needle electrodes in artificial and voluntary innervated muscle activity. Myographically they have shown a greatly diminished twitch response during the development of myotonic background contraction, with subsequent recovery to *twice* the initial twitch intensity, sometimes when the action potential has not yet recovered to initial value. These results are suggestively similar to those of Brown and von Euler[39] on tetanus potentiation of twitch responses. A related possibility is that some fibers are not initially available to neural excitation, as in avian muscle.[40] Brown and Harvey found no analogous changes during repetitive stimulation in goat myotonia.[14]

Lambert and Beckett concluded that the myotonic response pattern can be converted to normal with adrenaline.[23] Since no effect of adrenaline was seen in the present study, it appears that adrenaline affects only neurally excited myotonia, although the technique of Lambert and Beckett would not detect minor degrees of myotonia.

The results of this study agree with those of Brown and Harvey in considerable detail.[14] In particular, the "spontaneous" activity, sometimes of a synchronized nature, the mechanical irritability, the absence of a constant repetitive response to single nerve shocks, the gradual buildup of myotonia during repetitive nerve stimulation, with subsequent fatigue, and the absence of significant change after curarization and nerve block are also seen in goat myotonia. Brown and Harvey's observation that the myotonia appeared even worse at a period following nerve section when fibrillation appears in normal muscle emphasizes the close relation of these processes.[31] They also adduced critical evidence that there is hypersensitivity to potassium chloride, but none to acetylcholine or eserine, and concluded that the defect is in the muscle fiber itself. Confirmation of the beneficial effect of quinine[41] was also obtained. Kolb, however, could not obtain a sustained response to direct current stimulation, although it may have been obscured or poorly obtained with percutaneous stimulation. Clark et al. did not believe that the diseases in man and goat are entirely the same.[42]

In view of the general clinical picture of a wide spread metabolic disorder in myotonia dystrophica, it would appear possible that myotonic dystrophy is essentially a secondary phenomenon.[45] * Potassium ion metabolism may

*Dr. E. Ronzoni has performed duplicate 24 hour total neutral 17-ketosteroid determinations on three male patients. The values obtained were 1.4 and 2.0 mgm./24 hours, 1.5 and 1.6 mgm./24 hours, and 2.56 and 3.05 mgm./24 hours. The first patient had testicular atrophy and was apparently sterile. Apart from frontal baldness somatic hair growth was excessive. The second patient was similar except that somatic hair growth was not remarkable. The third patient had testicular atrophy but had one child born three years before the examination. There was no baldness or abnormal hair distribution. These values appear to indicate a degree of adrenal cortical as well as gonadal insufficiency.[44] Adie and Greenfield described pathologic changes in adrenal cortex and pituitary in myotonia dystrophica.[2]

logically be indicted by reference to Lambert and Beckett's work,[23] since the normal tetanus-potentiation of twitch responses was attributed to potassium mobilization.[39] No objective evidence that potassium ion worsens clinical myotonia has yet been presented.[11,33,36] The failure of DOCA in this study to produce improvement or even a significant fall in serum potassium would not oppose such a possibility. The failure of Cortisone with conventional dosage indicates that excessive requirement or deficient production of this hormone does not account for the condition.

This study confirms the symptomatic improvement with quinine reported by many observers, but it should be emphasized that quinine is non-specific therapy and does nothing for the large number of patients whose chief complaint is weakness rather than stiffness. It is evident that further study should be directed toward the essential metabolic abnormality in myotonic muscle. The high muscle acetylcholine and low cholineesterase found by Minz and Passouant[45] and the adrenaline effect shown by Lambert and Beckett[23] are interesting leads. The myotonic goat appears to be an ideal experimental subject.

SUMMARY

The phenomena of myotonia have been investigated electromyographically in six patients with myotonia dystrophica. It is concluded that the essential pathophysiologic defect in the disease is the hyperirritable repetitively responding muscle fiber; that there is no significant abnormality of neuromuscular transmission. The after-spasm phenomenon is apparently a physiologic response of the nature of a lengthening reaction in muscles stretched by persistent myotonic contraction in antagonists. There is no evidence that per se it is embarrassing to muscular movement.

The effects of curare, calcium gluconate, prostigmine, DOCA, Cortisone, adrenaline and quinine have been studied. The only drug which had a significant effect on the response to direct current in myotonia is the last, which depressed it considerably.

The relation of these studies to the basic metabolic disorder in myotonia has been discussed.

The advice and criticism of Dr. G. H. Bishop, who suggested this problem, and the assistance of Miss Margaret Clare are gratefully acknowledged.

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Cerebral Angiography in Diagnosis of Subdural Hematoma

Joseph M. Stein, M.D.

THE diagnosis of subdural hematoma is a common problem in a general hospital. A surgical procedure, trephination, is necessary to establish the diagnosis. Even with trephination subdural hematoma might be overlooked. In patients presenting signs and symptoms of neoplasm, pneumoencephalography is often employed and usually shows evidence of a mass lesion, but interpretation frequently can be no more specific. Thus the surgeon obtains guidance in the localization of the process but must be prepared for a variety of conditions during operation. Other problems in differential diagnosis arise with the concomitant presence of arteriosclerosis, hypertension and other conditions. A more specific diagnostic method would prove of value.

Since the investigation of subdural hematoma provides a frequent challenge on the wards of Bellevue Hospital, it was decided to study the problem by the method of cerebral angiography. A Cournand-Grino needle was used to puncture the common or internal carotid artery. In all cases the percutaneous route was used. From 10 to 12 ml. of 35 per cent Diodrast was used for each injection. The cassette holder provided one phase in the anteroposterior view and three phases in the lateral view. Fifteen patients suspected of subdural hematoma were injected, four under local and 10 under intravenous general anesthesia. Ten unilateral and four bilateral carotid angiograms were done.

Twelve men and three women from 26 to 58 years of age were studied. There was evidence of a head injury in each case. The findings varied and no syndrome could be considered pathognomonic of subdural hematoma. Neurologic states ranged from complete absence of signs to pronounced one-sided involvement and aphasia. The sensorium varied from very alert to markedly drowsy, and one of the patients was in coma. Spinal fluid findings were not diagnostic and extended from completely normal to bloody and xanthochromic fluid with increased protein and elevated pressure. Skull x-rays showed fractures in four cases and old burr holes in another case, thus providing evidence

From the department of neurology and psychiatry, Bellevue Hospital, New York City.
Presented at the combined meeting of the New York Neurological Society and Section of Neurology and Psychiatry of the New York Academy of Medicine, May 8, 1951.

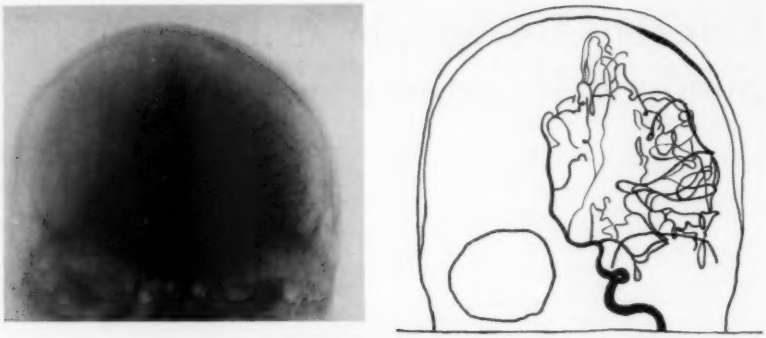

FIG. 1. Subdural hematoma. There is an avascular area under the entire cranial vault on the side of the angiogram and a marked shift of the anterior cerebral artery to the opposite side.

only of head trauma. A shifted pineal gland in one of the cases with a fractured skull indicated an intracranial mass but gave no clue to its exact nature. The subjects also had evidence of alcoholic encephalopathy, brain laceration, cerebral arteriosclerosis, hypertension, diabetic ketosis, pulmonary tuberculosis and schizophrenia, which complicated the diagnostic problems. In all cases it was desirable to rule out subdural hematoma in the presence of these differential diagnostic problems.

In each of the seven patients who had unilateral subdural hematomas when trephined the angiograms were abnormal. In this series there were no cases of bilateral hematoma. In six of these seven patients a specific angiographic pattern of an avascular space was seen. An anteroposterior view taken of the seventh patient was unsatisfactory because of motion and only a diagnosis of a mass lesion could be made. The characteristic pattern was revealed in the anteroposterior views of the arterial phase (figure 1). In this view there was an area which did not contain the vascular tree markings usually situated just beneath the cranial vault. Thus there was an avascular space adjacent to the cranial vault which extended for a centimeter or more into the cranial cavity. In addition the anteroposterior view showed a distinct displacement of the anterior cerebral artery to the opposite side. This view also showed some displacement of the middle cerebral artery, but this occurred only in cases with laterally situated hematomas. Most of the lateral views were considered to be within normal limits and none was of any diagnostic value. It is noteworthy that one of the cases showed the typical avascular space laterally, with compression of the middle cerebral tree, and in this case there was no displacement of the anterior cerebral artery (figure 2). One patient in this group died ten days after trephination and autopsy revealed diffuse brain edema but no recurrence of subdural fluid or blood. The remaining patients made satisfactory recoveries after surgery.

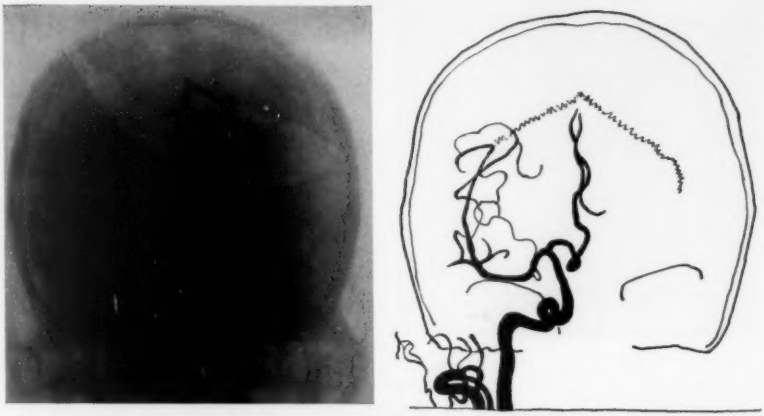

FIG. 2. Chronic subdural hematoma. There is compression of the middle cerebral arterial tree, with an avascular space between it and the cranium. Note that there is no shift of the anterior cerebral artery.

In eight patients suspected of subdural hematoma on clinical grounds the angiograms did not show the avascular space described above. One angiogram showed a vascular neoplasm, verified at autopsy. Another showed the pattern of an intracerebral mass, and a chronic intracerebral abscess was evacuated by the surgeon. Five others were not subjected to surgery and all improved. These five had pneumoencephalograms before discharge and in none was there any evidence of a space occupying lesion. One patient was in deep coma at the time of angiography, which was done under local anesthesia. He died about 36 hours later. At autopsy there was laceration of the brain and subarachnoid bleeding but no subdural collection was present.

Three representative cases are now described.

Case 6.—P. N., about 45 years old, was picked up on the street and there was no available history. On admission he was stuporous, his breath smelled of alcohol and he had no focal signs. His blood pressure was 170/110. Chest and skull x-rays were negative. Lumbar puncture showed grossly bloody fluid under 270 mm. pressure, with residual xanthochromia. After two weeks of observation the sensorium had improved somewhat but the patient was aphasic, with slight left lower facial weakness and a left Oppenheim reflex. An electroencephalogram showed a delta focus on the right. Repeat lumbar puncture showed clear xanthochromic fluid under 310 mm. pressure. Sixteen days after admission, right carotid angiography under general anesthesia revealed an avascular space under the vault of the skull and displacement of the right anterior cerebral artery to the left (figure 1). Left carotid angiography showed evidence of displacement from a mass on the right. A diagnosis of unilateral right subdural hematoma was confirmed by bilateral exploration. The patient recovered from all neurologic signs. Followup bilateral angiography five months later showed completely normal patterns on both sides. Pneumoencephalography after that showed only some generalized dilatation of the ventricular system.

Case 8.—J. S., a 26 year old girl, was admitted to a psychiatric ward with a history of heavy drinking for the previous week; no further history was available. On the follow-

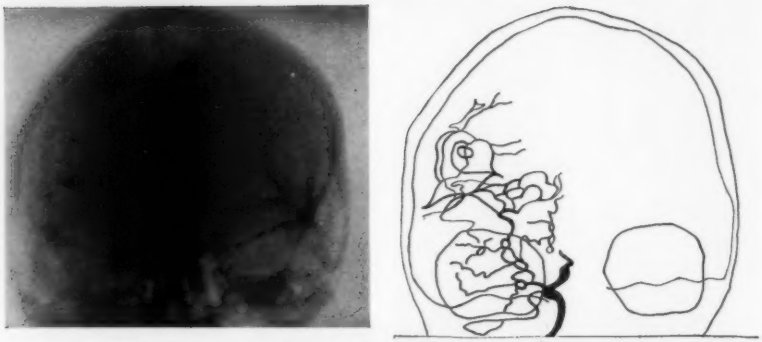

FIG. 3. Subdural hematoma in patient in diabetic ketosis. Avascular area is most marked laterally and inferiorly. Anterior cerebral artery is not well filled but is shifted to the opposite side.

ing day several convulsive seizures involving the mouth and both arms without loss of consciousness were observed. Neurologic examination on the fourth day was negative except for severe aphasia. On the sixth day progressive drowsiness began and the urine was discovered to show 4 plus glucose and 3 plus acetone. Chest and skull x-rays were negative and lumbar puncture showed faintly xanthochromic fluid under normal pressure, with a protein of 21 mg. and 6 crenated red blood cells. Examination demonstrated aphasia and right sided pinprick hypesthesia, but the patient was normal otherwise. While the diabetic ketosis was being treated, left carotid angiography was done under local anesthesia. The films showed an avascular space next to the temporal bone, compressing the middle cerebral tree in its lower portions, and a shift of the anterior cerebral artery to the right (figure 3). Immediate bilateral trephination revealed a very extensive hematoma on the left side. The patient responded dramatically and her diabetes was easily controlled with insulin. She was discharged with an improving expressive aphasia.

Case 10.—S. Y., a 34 year old woman, was known to be a severe alcoholic. She was reported to have been alert until found in a poorly responsive state by her husband on the evening before admission. Neurologic examination on admission was normal, but the marked lack of verbal contact left a differential diagnosis between functional psychosis and an organic mental syndrome. Laboratory examinations were normal except for a suspicious right sided hairline defect on skull x-ray. Lumbar puncture was completely normal. Because the patient did not improve, right carotid angiography was done under Pentothal anesthesia on the eighth day. It showed normal filling of both anterior cerebral arteries on the anteroposterior view and normal lateral views. The patient remained unchanged. A pneumoencephalogram was done and was normal except for some air under and possibly within the subdural space superiorly on both sides. Because it was felt that the air could possibly be outlining bilateral subdural collections, bilateral trephination was done and was negative. During the ensuing weeks more history became available. These facts and some further changes in the psychiatric status of the patient made a diagnosis of schizophrenia completely tenable.

DISCUSSION

Fifteen patients suspected of having subdural hematomas have been subjected to carotid angiography. The patients with hematomas had angiographic patterns which are considered to be specifically diagnostic. The surgeon was

able to proceed without delay and with reasonable certainty of finding a subdural hematoma. In addition, there were two cases in whom angiography demonstrated intracerebral masses. In one case, subsequent successful evacuation of a large brain abscess was then carried out. In another patient the angiogram showed clear evidence of a vascular neoplasm, providing accurate localization of the mass and information about its nature. The patient later expired and the diagnosis was confirmed at autopsy.

Equally important is the fact that it was possible to state definitely that there was no evidence of a subdural hematoma in six cases. These angiograms were all normal. Five of these patients were spared a surgical procedure. Another was trephined because of misleading air studies.

A series of diagnoses of subdural hematomas by angiography was described by Wickbom in 1949.[1] He also reported one case of epidural hematoma in which the pattern is the same. The pattern has also been described by Lima[2] and by others.[3,4] It is most important to emphasize that, although displacement of the anterior cerebral artery is common, it is not a constant feature. In a report published since this series was studied, the authors described a "false negative" angiogram in a case of bilateral subdural hygromas.[3] There was reported to be no displacement of the anterior cerebral arteries, but there was no mention of the presence or absence of avascular spaces. Wickbom specifically described this pattern, cautioning that when there is no shift of the anterior cerebral arteries bilateral collections must be suspected.[1] In one case in the present series, while bilateral angiography showed no shift of the anterior cerebral arteries, an avascular area on the right with displacement of the right middle cerebral tree proved to be diagnostic of a subdural hematoma.

That anesthesia and angiography itself provide risks is an important consideration. It has been our experience that these risks do not provide a contraindication in properly selected patients. However, for the patient rapidly progressing into coma in whom subdural hematoma is suspected, bilateral trephination under local anesthesia remains the procedure of choice. Patients in this condition require general anesthesia for angiography because they respond to painful stimuli by moving. It does not seem adivsable to cause further depression of the central nervous system in comatose patients.

It is our conclusion that angiography is indicated in cases of (1) difficulty in differential diagnosis involving intracranial masses, and (2) suspected subacute or chronic hematomas. The diagnostic advantages of angiography weigh in its favor and one can look forward to the following specific interpretations: (1) There is a subdural hematoma. (2) There is no subdural hematoma. (3) There is a mass which is intracerebral and the nature of which can frequently be determined. Remedial surgery can be hastened and can be more specifically adapted to the lesion.

SUMMARY

1. Fifteen patients suspected of subdural hematoma, in the presence of other major conditions and differential diagnostic problems, were studied

by percutaneous cerebral angiography.

2. Seven patients had verified subdural hematomas. In six of them the angiogram revealed a specific pattern. The seventh film was unsatisfactory because of motion, but a mass could be diagnosed nevertheless.

3. Of the remaining eight patients, angiography revealed a verified neoplasm in one and an intracerebral mass verified as a chronic intracerebral abscess in another. Five others with normal angiograms recovered, with subsequent pneumoencephalograms all negative for mass lesions. Another patient with a normal angiogram died from a verified cerebral laceration.

4. Cerebral angiography is proposed as a method for the specific diagnosis of subdural hematomas. Needless surgery can be avoided. In addition, it has the advantage of better localization of intracerebral masses and sometimes better definition of their nature.

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The true spinal diseases, especially those of eccentric origin, affect, in a remarkable manner, the set of functions which I have noticed as belonging to this system: those of the eye and eye-lid; those of the larynx, of the pharynx; the respiration; the action of the expulsors and of the sphincters; that of the muscles designated by the term *tone*. Revolve in your mind the symptoms of epilepsy; of hysteria; of tetanus; of hydrophobia; the causes and phenomena of vomiting, of asthma, of abortion, of tenesmus, and of strangury, and you will be forcibly struck with the justice of this remark. On the other hand, every convulsive effort affects the brain with congestion and its consequences, of which a fatal coma or effusion are not the least frequent.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

Hypnosis in Differentiation of Epileptic From Convulsive-like Seizures

John W. Sumner, Jr., M.D., Richard R. Cameron, M.D. and Donald B. Peterson, M.D.

A PRELIMINARY STUDY of 65 consecutive cases of either epileptic or psychogenic convulsive disorder has been reported.[1] A second identical series of 77 consecutive cases has been set up, and the scope of the investigation broadened so that a separate group of 33 patients with alcoholic, organic or syncopic seizures is presented.

The original technique and rationale have been retained. The hypnotic recall technique is practicable because persons with psychogenic seizures hypnotize more easily and in greater proportion than reported for the general population. This technique utilizes the fact that, unlike the epileptic who has an absolute amnesia for the details of his convulsive seizures, the psychogenic seizure patient is capable of attention and memory during his seizure and can recall such memories under hypnosis. In brief, the hypnotic recall technique is of diagnostic usefulness in hypnotizable seizure patients who profess an amnesia for all or part of their seizure. The epileptic's conscious description of his seizure is identical with his hypnotic description, whereas the psychogenic's consciously-described amnesia vanishes under hypnosis.

All patients presenting a convulsive disorder were admitted to the neurology section and subjected to a standardized workup which included history; physical, neurologic and laboratory examinations; skull x-rays and sleep electroencephalograms. Efforts to hypnotize each patient were made. The hypnotist knew only that the patient was in the epilepsy project and was deliberately kept in ignorance of any other findings. His was the task of securing a detailed history, delineating the boundaries of the amnesia associated with various seizures, and among the hypnotizable, determining whether or not the patient could recall memory for the events that occurred during the amnesia period of the seizure.

The statement that the diagnosis of epilepsy is more difficult than is commonly appreciated is well worth repetition. Further, it is believed that the

From the sections of neurology and psychiatry and the neuropsychiatric service, Fitzsimons Army Hospital, Denver, Colorado.

Read at the American Psychiatric Association meeting, Cincinnati, Ohio, May 1951.

incidence of psychogenic seizure of generalized nature is much higher than is commonly appreciated. Reports of large groups such as that of Rossen[2] are all too few. In a group of 469 navy personnel admitted because of seizures, he found that the seizures of 209 or 44 per cent were not epileptic. It appears that about half of convulsive seizures are psychogenic.

Penfield's classification of the epilepsies[3] is a forward-looking attempt to leave the field of advancement in differential diagnosis open so that equivocal or ambiguous cases may be excluded from known categories.

It has been reported that not infrequently epileptic and psychogenic seizures occur in the same patient.[4–6]. Such a patient presents an intricate diagnostic and therapeutic problem. The patient's dosage and type of anticonvulsant medication may be altered repeatedly because unrecognized psychogenic seizures may cause his epilepsy to be regarded as poorly controlled. On the other hand, if only the psychogenic seizure is recognized, particularly where the epileptic seizures are infrequent, psychotherapy may be unduly prolonged.

Edelston[7] asserts that there are mixtures of epilepsy and hysteria, that such cases are usually diagnosed epilepsy, and that too few such cases are reported. Therefore it seems worthwhile to present the following case.

CASE REPORT

A 24 year old white private was admitted to Fitzsimons Army Hospital on December 8, 1950, with transfer diagnosis of "epilepsy, grand mal." Convulsive seizures began in 1944 at the age of 16. In August 1944 he enlisted in the navy, was hospitalized within one month, and given a medical discharge because of epilepsy. Convulsive seizures continued to occur every five months or so. On November 6, 1950 he was inducted into the army. The following day was rather strenuous due to processing. He stated that in the evening while in the barracks he felt dizzy, missed a step into the latrine, and then lost consciousness. Fellow soldiers took him to the hospital where he regained consciousness. A few hours later he had a grand mal seizure with clonic and tonic movements of all extremities, dilated pupils, tongue-biting, and postictal bilateral Babinski signs. This seizure was witnessed by an army nurse and a medical officer. The night of November 15, 1950 he had another generalized seizure witnessed by the medical officer of the day which followed generally the same pattern as the previous one. The patient was transferred to Fitzsimons Army Hospital for further observation and treatment.

Physical, neurologic, laboratory and x-ray examinations were normal. A sleep electroencephalogram was abnormal. The patient had conscious amnesia for all three seizures. The patient was hypnotized to somnambulism and under hypnosis was able to recall in complete detail the first seizure he had in the barracks prior to hospitalization. He remembered falling, hitting his forehead on the trough of the urinal, and then rolling on the floor. He recalled another soldier's asking him, "What are you doing on the floor?" and his reply, "I fell off the step as I didn't see it." Under hypnosis he was unable to recall any of the details of the second seizure witnessed in the hospital November 7, 1950. However, under hypnosis he had complete recall for the third seizure witnessed in the hospital November 15, 1950, including thrashing around, waking up other patients in the ward, falling out of bed, and being lifted back into bed.

COMMENT

Thus we have a patient with a history of seizures since age 16 who in November 1950 had three convulsive seizures. The electroencephalogram

was abnormal. Under hypnosis he recalled all details of two of his seizures, one of which was witnessed, but no details of the other seizure witnessed by a medical officer and a nurse. It is believed that this patient has both psychogenic seizures and grand mal epilepsy.

It is hard to overestimate the therapeutic importance of determining within a few days that this patient had both epileptic and psychogenic seizures. There is no other diagnostic technique by which this can be accomplished so quickly, accurately and easily.

The purpose of this presentation is not merely to add cases to those reported previously, although the total number of cases is presented and analyzed. The prime purpose is a statistical comparison of the two consecutive series. This is particularly valuable since, if the two series compare closely, there is a strong probability (1) that the number of cases in each series is great enough to be significant, and (2) that the hypnotic recall technique offers considerable reliability. On the other hand, a poor correlation between the two series would indicate the reverse. If the two groups correlate closely enough to indicate reliability, the presentation of ratios derived from the total is warranted because of the increased accuracy inherent in a larger group.

GENERAL CONSIDERATIONS

The findings are generally presented in tabular form and comparison will be made between the 1949 and 1950 series which hereafter will be referred to as Series I and Series II, respectively. It must be borne in mind that all patients were admitted because of some seizure or convulsive disorder, which makes for quite a select group of the population, and that the statistics derived relate to this group or its subgroups rather than to the general population.

Certain definitions are necessary. The total seizure patient group is divided into organic, syncopic, alcoholic, epileptic and psychogenic. These subdivisions are generally self-explanatory. Syncope is included because it enters into the differential diagnosis, and the three cases included were transferred to this hospital with a working diagnosis of epilepsy. All of the epileptic group had either grand or petit mal seizures or a combination of the two, the great preponderance being grand mal. There was none whose seizures were exclusively psychomotor.

Abnormal electrocardiographic findings consist of abnormal paroxysmal and borderline records. The borderline records are those which show cerebral dysrhythmia compatible with, but not diagnostic of, epilepsy.

Hypnotizability refers to the ability to be hypnotized to somnambulism. Recall is defined as the ability, while in the hypnotic state, to recall the details of the seizure; that is, to recapture the memory of thoughts, feelings and happenings which occurred during that part of the seizure for which the patient is consciously amnesic.

Admittedly these categories of epileptic and psychogenic seizures are subject to the hazard of diagnostic error. It is evident that in diagnosis both the electroencephalogram and the recall technique were relied upon, and an

attempt is made to show the latter to be of diagnostic importance. Obviously, since recall is used in making the diagnosis, one cannot use the diagnosis arrived at as a method of validating the recall. It is essential that particular attention be paid to correlations between the electroencephalogram and recall, both of which are objective findings independent of diagnosis.

Alcoholic seizures are defined as seizures occurring in association with alcoholic episodes either during the acute alcoholic state or during the "hangover" period in patients who have no convulsive seizures under other circumstances.

An excellent summary on alcoholic and other non-epileptic seizures was made by Kalinowsky in 1942.[8] From the literature it is apparent that alcoholic seizures seem to be a withdrawal effect, that abstinence from alcohol results in freedom from seizures, and that a person with alcoholic seizures does not progress into an idiopathic epilepsy. Geddes,[9] in a preliminary report on the effects of drinking in 25 patients whose generalized convulsions antedated their alcoholism, found that only three felt that alcohol would precipitate a seizure, and that such seizure would occur within 24 hours of the drinking. He concluded that in most adult epileptics drinking had little or no effect on the frequency or severity of seizures. Cure, Rasmussen and Jasper,[10] in their studies on activation of seizures, stated that while alcohol might induce seizure in certain patients it was very uncertain. Greenblatt[11] reported 24 patients as having "rum fits," regarded these alcoholic seizures as a separate entity, and found electroencephalographic abnormality in only 17 per cent. Lennox[12] gave alcohol as a primary cause of seizures in 2.1 per cent of intramural epileptics. It seems evident that alcohol, in some way, will produce seizures in certain persons during drinking or on withdrawal, but that alcoholic seizures are not of the same order as, nor do they become, idiopathic epilepsy. Therefore one feels justified in treating our alcoholic seizure group separately.

FINDINGS

1. The alcoholic, organic and syncopic seizure groups of the combined series, totalling 33 cases, are correlated with electroencephalograms, hypnotizability and recall in table 1. Results in these groups were exactly as expected. In the alcoholic group all electroencephalograms were normal, and of the 13 alcoholics only one hypnotized and he did not recall the detail of his seizures. Of the 17 organic patients, five hypnotized and did not recall, and of the three syncopics, two hypnotized and did not recall. The normal record in the alcoholic group is in accord with the findings of others and it is apparent that were this group not separated from the epileptic, the abnormal electroencephalogram rate for the epileptic group would be lowered. These 33 cases are in addition to the 142 which form the basis of further discussions.

2. The general intelligence of the 142 epileptic and psychogenic seizure patients in the combined series is correlated with hypnotizability in table 2. This table is presented primarily for the record, but here it must be remembered that this population is unusual in that it is a convulsive seizure popula-

TABLE 1

	SEIZURE GROUPS								
	Alcoholic			*Organic*			*Syncopic*		
Hypnosis / *Recall*	*Hyp.* Yes	*Hyp.* No	*No*	*Hyp.* Yes	*Hyp.* No	*No*	*Hyp.* Yes	*Hyp.* No	*No*
Abnormal EEG	0	0	0	0	3	6	0	0	0
Normal EEG	0	1	12	0	2	6	0	2	1
Total	0	1	12	0	5	12	0	2	1

tion. The high, medium and low groups show an incidence of hypnotizability respectively of 19 out of 37, 44 out of 66, and 26 out of 39, or 51, 66 and 67 per cent. The overall hypnotizability without regard for intelligence level for Series I is 45 out of 65, or 69 per cent; for Series II is 44 out of 77, or 57 per cent; and for the combined series is 89 out of 142, or 63 per cent.

TABLE 2

	INTELLIGENCE											
	High			*Medium*			*Low*			*Total*		
	I	II	I+II	I	II	I+II	I	II	I+II	I	II	I+II
Hypnotizable	12	7	19	26	18	44	7	19	26	45	44	89
Non-hypnotizable	8	10	18	6	16	22	6	7	13	20	33	53
Total	20	17	37	32	34	66	13	26	39	65	77	142
Per cent hypnotizable	60	41	51	81	53	66	54	73	67	69	57	63

3. Of the total 142 patients, 89 were hypnotized, and these 89 constitute table 3 in which their ability to recall is correlated with the electroencephalogram. Of those who could recall, the record was abnormal in one out of 25 or 4 per cent; in Series I, in two out of 25 or 8 per cent in Series II, and in three out of 50 or 6 per cent in the combined series. Of those who could not recall, the record was abnormal in 18 out of 20 or 90 per cent in Series I, in 18 out of 19 or 95 per cent in Series II, and in 36 out of 39 or 92 per cent in the combined series. These series are identically structured and consecutive. Since the parallelism between the two is so great and the parallelism is evident in both the recall and non-recall groups, it is apparent that there is more than coincidence involved. It is believed that the approximate duplication of results in the two consecutive series is indicative of the reliability of the previously reported findings — namely, that recall and an abnormal electroencephalogram almost never occur together. Further, it is fair to say that non-recall in the hypnotizable and a normal record are also almost mutually exclusive.

4. Diagnosis is correlated with electroencephalograms in table 4, consisting of 142 seizure patients derived from adding the 53 non-hypnotizable to the

TABLE 3

Electroencephalogram	HYPNOTIZABLE						
	Recall			*Non-Recall*			
	I	II	I+II	I	II	I+II	
Abnormal Paroxysm	1	2	3	16	15	31	34
Borderline	0	0	0	2	3	5	5
Total Abnormal	1	2	3	18	18	36	39
Normal	24	23	47	2	1	3	50
Total Patients	25	25	50	20	19	39	89
Per cent Abnormal	4	8	6	90	95	92	44

89 hypnotizable patients discussed above. This group has been divided into epileptic and psychogenic seizures. Each group has been divided into the hypnotizable and non-hypnotizable, and the hypnotizable have in turn been divided into those who recall and those who do not recall.

TABLE 4

Series	EPILEPTIC									PSYCHOGENIC								
	Hypnotizable						*Not Hyp.*			*Hypnotizable*						*Not Hyp.*		
	Recall			*No Recall*						*Recall*			*No Recall*					
	I	II	Comb	I	II	Comb	I	II	Comb	I	II	Comb	I	II	Comb	I	II	Comb
Abn. Parox.	0	0	0	16	15	31	7	19	26	1	2	3	0	0	0	0	0	0
Borderline	0	0	0	2	3	5	3	2	5	0	0	0	0	0	0	0	2	2
Total Abn.	0	0	0	18	18	36	10	21	31	1	2	3	0	0	0	0	2	2
Normal	0	0	0	2	1	3	0	2	2	24	23	47	0	0	0	10	8	18
Grand Total	0	0	0	20	19	39	10	23	33	25	25	50	0	0	0	10	10	20
Per cent Abnormal				90	95	92	100	91	94	4	8	6				0	20	10

Of the epileptic seizure group who hypnotized, not a single one recalled, while of the psychogenic group who hypnotized not a single patient did not recall. Of the epileptics who hypnotized and could not recall, in the first series the electroencephalogram was abnormal in 18 out of 20, or 90 per cent; in the second series in 18 out of 19, or 95 per cent; and in the combined series in 36 out of 39, or 92 per cent. Of the epileptics who did not hypnotize the record was abnormal in the first series in 10 out of 10, or 100 per cent; in the second series in 21 out of 23, or 91 per cent; and in the combined series in 31 out of 33, or 94 per cent. Of the psychogenics who hypnotized and did recall, the record was abnormal in the first series in one out of 25, or 4 per cent; in the second series in 2 out of 25, or 8 per cent; and in the combined series in 3 out of 50 or 6 per cent. Of the psychogenics who did not hypnotize

the record was abnormal in the first series of 0 out of 10, or 0 per cent; in the second series in 2 out of 10, or 20 per cent; and in the combined series in 2 out of 20, or 10 per cent.

From this table it is easily calculated that in those diagnosed epileptic, 93 per cent had an abnormal electroencephalogram, and in those diagnosed psychogenic, 7 per cent had an abnormal record. It is also easily calculated that 55 per cent of the epileptics and 71 per cent of the psychogenics were hypnotizable, and further that 71 per cent of all patients with normal records were hypnotizable. This indicates a very utilitarian prevalence of hypnotizability where it is needed most – namely, in 71 per cent of those who have convulsions in the face of a normal record.

5. The correlation between admission or transfer diagnosis and the final diagnosis is quite interesting. No criticism of the transfer diagnosis is implied because in the differential diagnosis of states of unconsciousness or convulsion, epilepsy is always to be ruled out, and it is approved practice to refer such cases to a general type hospital for diagnostic procedures where electroencephalographic facilities are available. This transfer is deliberately accomplished speedily with a minimum of workup, and the transfer diagnosis quite rightly and inevitably is based on clinical impression, which in turn must often be based on the testimony of an excited witness. A diagnostic distribution of cases so referred is interesting and important. In the epileptic group there was a 99 per cent correlation between admission and final diagnosis. Seventy-one of the 72 cases of epilepsy were called "epilepsy" on admission. In the psychogenic group there was but a 13 per cent correlation. Nine of the 70 cases carried a diagnosis of "psychogenic seizure" on admission, and the other 61 carried some such diagnosis as "observation, epilepsy."

The final diagnostic distribution of the two series was very close. In Series I there were 30 epileptics to 35 psychogenics. In Series II, 42 epileptics to 35 psychogenics, giving a combined series ratio of 72 epileptics to 70 psychogenic.

DISCUSSION

1. The detailed rationale behind the hypnotic recall technique is not discussed since it has been described elsewhere.[1]

2. It is believed that the alcoholic seizures are apt to slip into the epileptic group where they serve as a contaminant, and it is thought desirable to call attention to the difference between the two groups since the present findings corroborate the reports of others.[8,11] Further, the treatment regime with regard both to medication and prohibition of alcohol hinges on differentiating these two groups from one another.

3. A case of combined epileptic and psychogenic seizure is presented to point up this particular diagnostic and therapeutic problem, and to indicate that the hypnotic recall technique offers much in the way of early recognition of this combination.

4. Certain questions are brought to mind. Often one is asked whether or not patients will lie under hypnosis. Of course the answer is that some

patients certainly will. However, the figures speak for themselves, and demonstrate the reliability of this technique. The question of skill of the hypnotist presents itself. Skill is never to be decried, but it is felt that less skill than interest is involved in this procedure.

CONCLUSIONS

1. The present findings corroborate the work of others indicating that most patients with alcoholic convulsions have a normal interseizure electroencephalogram, and that alcoholic seizures should be considered a separate entity.

2. Hypnotizability is found in approximately two out of three patients who present convulsions despite a normal electroencephalogram.

3. There is an extremely close correlation between the previous series of seizure patients and the present one, both subjected to identical selection investigation, and statistical analysis indicates that the hypnotic recall technique has a high degree of reliabiliy in the differentiation of epileptic from psychogenic seizures.

4. Hypnotic recall technique offers a quick and easy method for identifying the patient with combined epileptic and psychogenic seizures.

SUMMARY

An analysis was made of a second series of 77 cases of epileptic or psychogenic seizure and compared with the original analysis of 65 cases. The electroencephalographic record, hypnotizability and ability to recall the details of seizure under hypnosis were correlated and indicated that the hypnotic recall technique has both validity and reliability in differential diagnosis.

Thirty-three cases of alchoholic, organic and syncopic seizure were presented with findings that suggested that alcoholic seizures are an entity separate from idiopathic epilepsy.

A patient with combined epileptic and psychogenic seizures is reported.

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Mesantoin in the Control of Epilepsy

Anthony E. Loscalzo, M.D.

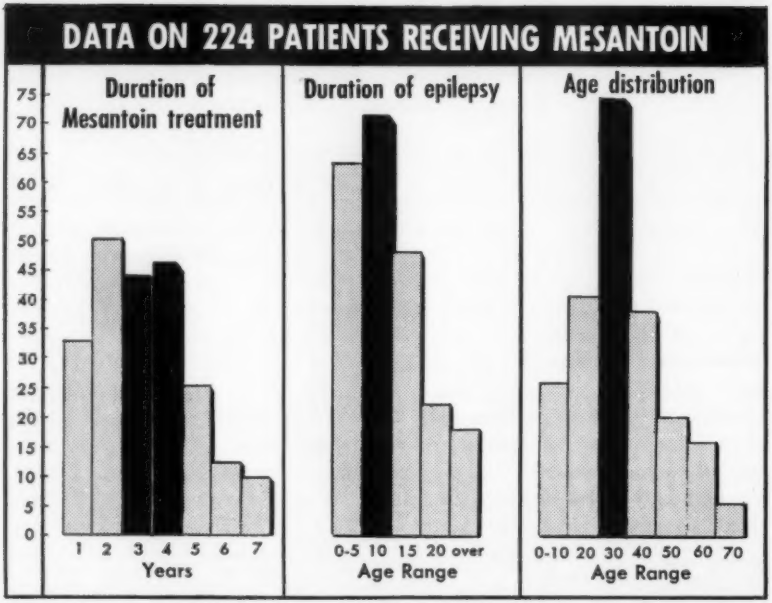
REVIEW OF LITERATURE

SINCE publication of the first reports[1,2] on the use of a new anticonvulsant, 3-methyl-5,5 phenylethyl hydantoin (Mesantoin), much has been published on its value in the treatment of epilepsy. Many of the reports[3–13] review the over-all factors involved, i.e., psychotherapy, occupational therapy, family cooperation, surgical methods, etc. They also compare the relative efficiency of each available chemotherapeutic agent for the various types of epilepsy.

Many pharmacologic studies,[14,15,16,17] as well as some reports on electroencephalographic studies[18,19,20] following the use of this drug have also appeared. Swinyard[17] and his group, in studies dealing with the causes and prevention of seizures, have shown that Mesantoin possesses a strong anticonvulsant action in electrically induced convulsions in laboratory animals. Lennox[19] believes that medication may influence the seizures as an "externalizing mechanism," before it influences the dysrhythmia of an inter-seizure recording. It is often difficult to study the effect of medication with electroencephalograms, so for the present these studies are mainly of academic interest.

Favorable clinical results have been reported in most studies.[21–31] Incidence of control of seizures varies, but the greater percentage of patients obtained a satisfactory degree of beneficial results. The literature indicates that Mesantoin has proved more effective than phenobarbital alone, and some authors believe it is a better antiepileptic. Others prefer Dilantin (diphenylhydantoin sodium) for the control of seizures. There is still another group who feel that the two drugs are about equal in their anticonvulsant action. Mesantoin apparently has the milder side effects so that larger doses can be safely tolerated.[21] If smaller initial doses are used in sensitive patients, gradual increase in dosage (in accordance with the needs of the patient) will yield maximum therapeutic benefit with a minimum of toxic effects.[22] Dyer[25] reported that best results were obtained by gradually increasing dosage until the anticonvulsant limit was reached. If previous medication had been used,

From the Clinic for Convulsive Disorders, St. Clare's Hospital, New York City.



it was decreased as the Mesantoin dosage increased. Mesantoin in combination with phenobarbital (Hydantal) proved effective in the treatment of grand mal, psychomotor and focal types of epilepsy.[23] This anticonvulsant was also used to treat hospitalized male psychotic epileptics with improvement noted in 14 out of 15 patients.[26] Mesantoin had no effect on the mental faculties. On the contrary, its initial action was often excitatory, thus requiring small doses of phenobarbital for counteraction.[28] Kozol[29] reviewed a series of 200 patients treated over a period ranging from three months to four years. Only 12 per cent of these cases remained unimproved. It should be noted that many patients in this latter group did actually show some improvement but it was insufficient to be classified in the two improvement "groups".

EFFICACY OF MESANTOIN IN THIS STUDY

This study reports the effect of Mesantoin therapy in a group of 224 clinic and private patients treated over a period ranging from one to seven years (figure 1). Of these patients, 50 were included in an interim report.[2] The 174 additional patients had previously been taking Dilantin, of whom 156 (almost 90 per cent) were taking it in combination with phenobarbital. As previously reported,[2] many patients taking hydantoin drugs require the addition of a barbiturate preparation. By interchanging Mesantoin with Dilantin and maintaining the amount of barbiturate constant, a valid comparison of

the clinical effects of the two was made possible. At the same time the patient's medication was not too greatly disturbed, for the anticonvulsant action of phenobarbital was preserved under the new conditions: The predominant types of seizures treated are summarized in table 1.

TABLE I

Type of Seizure	*Number of Patients*
Grand mal	154
Psychomotor	30
Petit mal	24
Focal convulsions	10
Jacksonian	6

Of the 24 patients who suffered predominantly from petit mal seizures, only 10 had never had grand mal attacks. The petit mal cases were subjected to a reasonably long period of trial on Mesantoin before other drugs of proven efficacy in petit mal seizures were added to their therapeutic regimen. Such drugs as Tridione (½ Gm. to 2 Gm. daily) and Paradione were employed as adjuncts, and a more careful and frequent check on the complete blood counts of these patients was kept.

Etiology of the epilepsy was undetermined in 160 patients. The remaining 64 had acquired epilepsy from such probable causes as skull trauma, birth injuries, arteriosclerosis, Alzheimer's disease, cortical degeneration, etc. Two sisters suffering from familial spinal spastic paralysis (cerebral type) were also included. A subsequent report will deal, in greater detail, with such aspects of epilepsy as etiology, diagnosis and prognosis.

Dosage: All patients were given the same number of Mesantoin tablets as they were taking of the Dilantin capsules, with the amount of phenobarbital remaining unchanged. Most patients were already taking a maximum tolerable amount of Dilantin; beyond their established dosage, toxic symptoms had appeared. In fact, this had led many of the patients to the clinic for further aid. After 8 to 12 weeks of this therapy, dosage was modified in order to obtain optimum therapeutic effect. The range varied from one to ten tablets daily of Mesantoin, with an average daily dose of five tablets (0.5 Gm.) and about 1¾ grains of phenobarbital. The above procedure clearly indicates how phenobarbital was used as a common denominator.

Expected incidence: The efficacy of therapy was based (as previously)[1,2] on the number of attacks following Mesantoin therapy as compared to the number of seizures prior to treatment. The expected monthly incidence is calculated by dividing by 12 the total number of grand mal seizures in the 12 months just previous to starting the medication. If this figure is assumed to be 1, then the expected total number of seizures would be 12 for the first year of Mesantoin therapy. The actual number of seizures during the first year of treatment is compared to this figure, thus showing the effectiveness of medication on the number of expected seizures. It must be emphasized

that spontaneous remissions occur which may complicate any study of the therapeutic effect of an anticonvulsant. Spontaneous remissions can hardly play a role in those cases in which the beneficial effect follows almost immediately after starting a new drug. In order to offset the possibility of a spontaneous remission, the dosage of Mesantoin was deliberately reduced in some cases who had no seizures for a long period of time. In almost all patients whose dosage was reduced, reappearance of grand mal seizures occurred.

Clinical results: The total expected incidence of grand mal seizures for all patients was 8,379. The actual total number of seizures of all patients was 4,228. This is a reduction of slightly less than 50 per cent as compared to the incidence of seizures prior to starting Mesantoin. These results do not include other types of seizures since no attempt was made to keep actual counts of Jacksonian, psychomotor and petit mal episodes. In the interim report,[2] the reduction in expected grand mal seizures was approximately 60 per cent. The difference between the two results may be explained by the fact that this is a larger group studied over a longer period and includes more refractory cases than previously.

Grand mal seizures were completely abolished in 66 cases; reduced from 10 to 90 per cent in 116 patients; the same as previously in 22 cases; and increased in 20 cases. Little or no effect was observed in petit mal, in fact, in some cases seizures were increased. There appeared to be a slight decrease in the number of psychomotor seizures, but not statistically significant.

SIDE EFFECTS AS REPORTED IN THE LITERATURE

The use of a new drug always necessitates great care since it may, in itself, produce undesirable side effects which may have dangerous consequences. The early reports on Mesantoin, based on shorter periods of observation, were optimistic, since most of them failed to mention the possibility of toxicity of the new hydantoin. With greater usage, some studies appeared reporting the toxicity of this drug. There are three types of untoward reactions that may be observed as a result of this medication.

Skin reaction: This side effect has been observed by many investigators.[2,22,29,32–36]. Various clinicians have reported an eruption either eczematoid, urticarial, acneform or seborrheic in nature. If such occurs, it usually does so within the first few weeks of treatment. Kozol[29] reported an exfoliative dermatitis in 1 per cent, but he did observe a morbilliform or scarlatiniform rash in 6.0 per cent of his 200 cases. Many of these patients were desensitized by starting again on smaller doses. There have been two severe skin reactions reported.[35,36] One of these patients[35] died of fulminating dermatitis bullosa, the other survived. Precautions to be taken when treating an epileptic with Mesantoin have been described.[37]

Drowsiness and other central effects: These have been reported in several instances.[2,29,32,38,39]. Kozol[29] employs the degree of drowsiness as an end point of medication. Deutsch[38] carried out a complete liver function study on a

series of 33 patients and found no evidence which necessitated the discontinuance of Mesantoin therapy.

Hematologic changes: There have been several reports that Mesantoin causes blood dyscrasias. Aird[40] reported a death from aplastic anemia. Another case of fatal aplastic anemia with a sudden and acute onset was reported by England.[41] Bloom[42] reported a case of aplastic anemia that recovered. Weller and Metcalfe[44] reported a fatal case of pancytopenia, and Davies et al[45]. reported one that recovered. Best and Paul[43] also treated a case of aplastic anemia that recovered.

These studies point out the possible untoward effects of Mesantoin medication. As yet, no one has found a definite relationship between skin rash and blood dyscrasia. However, several of the fatal hematologic cases had developed an earlier skin reaction.[45] Certain precautions must be taken which will be pointed out later in this report. Schwab and Abbott[46] in their recent paper discussed several factors which aid in reducing toxic effects of the newer anticonvulsant drugs in general. They emphasize that the physician must be on the constant alert for blood changes, liver changes or any other variations that may indicate undesirable effects from any of the newer drugs.

CLINICAL OBSERVATIONS IN THIS STUDY

The following side effects were observed in the present series of 224 patients:

Drowsiness	36	(16%)
Rash	22	(9%)
Gingival hypertrophy	7	(3%)

The marked cases of drowsiness were moderately relieved by Benzedrine. Of the seven patients with gingival hypertrophy, four were children under 12 years of age.

Rash: Kozol[29] reported a rash incidence of 6.0 per cent. It is interesting to note that he employed a small initial dosage of Mesantoin with gradual increase to the therapeutic level. The method reported here differs, in that almost full thrapeutic doses of Mesantoin were used at the start of treatment. The fact that there is no marked difference in rash incidence between the two methods of initial dosage indicates that side reactions may be a matter of individual patient sensitivity and susceptibility and not one of toxicity per se.

In all 22 patients, the rash developed before the fourth month of continuous therapy. Six were children ranging in years from seven to 11. One child and six adults had suffered from previous drug rash (sulfonamides). One child gave a history of bronchial asthma. A group of four adults had had previous rash of undetermined origin. The remaining 10 cases (four children and six adults) had no previous history of rash or allergy.

Some clinical notes on the rash:

1. In all patients the rash was generalized, pruritic and morbilliform, lasting one to three weeks.
2. In all cases there was some elevation in temperature which lasted three to five days, highest in the children.

3. Adenopathy was observed in all six children, and in eight of the 16 adults.
4. Mild exfoliation followed subsidence of the fever and rash in four children and four adults.
5. Definite symptoms of acute upper respiratory infections were present at the time that the rash appeared in four children and in only three adults.

Two other interesting observations:

1. Moderate hypertrichosis was seen in three children.
2. Slight increase of skin pigmentation was observed in two children. This is an unusual reaction and has not been, as yet, reported by other investigators.

Blood changes: In view of the reported cases of pancytopenia, complete blood counts (including platelet counts) were made on 180 of this series of 224 patients, although all patients had had initial blood studies. Results showed that in 12 cases (6.7 per cent) the white cell count was below 6,000. In 10 (5.5 per cent of 180) of the 12 cases the red cell count was below 4 million, hemoglobin was between 10 and 11 Gm., and the platelet count ranged from 100,000 to 170,000. None of the 12 cases exhibited any rash or other untoward reaction. Four of the 10 had been taking Mesantoin for longer than a year, and six for less than a year.

One patient (female, 22 years old) who had been on Mesantoin medication with excellent results for two years had the following count: RBC, 3,000,000; W.B.C., 3,000; hemoglobin, 9.2 Gm.; neutrophiles, 40 per cent; platelets, 115,000. Her daily dosage of 0.4 Gm. (4 tablets) was continued. In addition, she was given 4 capsules daily of ferrated liver. A blood count six weeks following the above count showed: R.B.C., 3,600,000; W.B.C., 4,020; hemoglobin, 10.2 Gm.; neutrophiles, 52 per cent; platelets, 140,000. On questioning the patient, the only significant abnormality was a change in the nature of the menstrual flow for the three months previous to the first blood count. The menses had been heavy and prolonged, which was very unusual for this patient. Following the last blood count her menses were again normal. This patient has shown no other untoward effects and is being continued on Mesantoin, since the drug is most effective in controlling her seizures. She is also being re-checked very carefully.

DISCUSSION

Clinical results: In this study Mesantoin has proven to be a most efficient antiepileptic drug. It is indicated: for cases that develop toxic symptoms to Dilantin, phenobarbital or other anticonvulsant drugs; for cases that are not adequately controlled by other drugs; and for all new suitable cases of grand mal epilepsy.

Best results are obtained if dosage is adjusted carefully to suit the individual needs of each patient. Each case must be evaluated carefully and treated accordingly. It is important to determine severity of the seizures and any previous medication. A patient with no previous drug sensitivity or allergic history may be started with a larger dosage than one who has had such a background. In changing from one of the other antiepileptics, it is the author's practice to make the change an abrupt one, providing no contra-

indications exist. No significant ill effects or unusual increase in the number of convulsions has been observed employing this method.

Phenobarbital has been found to be a useful adjunct to Mesantoin therapy. Four to five tablets of Mesantoin of 0.1 Gm. each daily is considered an adequate dose in most patients. Should a new patient continue to have the same number of seizures with it as before, a small amount of phenobarbital is added to his daily drug intake. A daily quantity of 0.04 to 0.06 Gm. phenobarbital is usually sufficient to achieve a reduction or freedom of seizures. Approximately 90 per cent of the patients reported here were already taking phenobarbital when first seen and were continued on the same dose, which was adjusted later if necessary. It may be dangerous to stop phenobarbital suddenly in a patient accustomed to taking it over a period of many years. Sudden cessation of phenobarbital can bring on an increase in the number of seizures, increased nervousness, insomnia, restlessness, and in some instances, status epilepticus. However, a patient taking extremely large doses of phenobarbital cannot be initiated safely on Mesantoin therapy until the phenobarbital dosage has been reduced sufficiently to make it possible to add Mesantoin gradually to the regime. Serious complications may result from the additive effect of several drugs in high dosage.

Toxicity: In our experience Mesantoin has a better clinical anticonvulsant action than Dilantin. It is generally less toxic than other hydantoins and it can be increased to larger doses with better therapeutic results. Unfortunately, in a small number of sensitive individuals severe reactions (as well as death) have been reported. It is possible that Mesantoin reactions are due to an individual sensitivity and in extremely sensitive individuals, dangerous reactions can occur. In susceptible patients, initial daily dosage must be small and gradually increased at bi-weekly intervals.

The number of unfavorable reactions can be kept at a minimum by adopting a cautious and careful program. The following are indication for such an approach: patients giving histories of previous drug reactions (especially sulfa drug reactions) regardless of the type of reactions or nature of the drug; patients having histories of previous rash regardless of etiology; patients who have never taken drugs of the hydantoin group; patients requiring 0.8 Gm. or more daily; patients giving histories of allergy.

Mesantoin therapy must be discontinued immediately and further investigations started at the following warning signals: rash of any type—including purpura and ecchymosis; vaginal bleeding, whether of the menorrhagic or metrorrhagic variety; bleeding from the gums; sudden unusual loss of weight. Other early warnings calling for prompt investigation and reduction of medication are: pruritus—whether generalized or localized; lacrymation; "canker sores"; postauricular exfoliation.

Mesantoin is definitely contraindicated in patients whose initial total white blood cell count is 4,000 or lower. Patients who develop acute upper respiratory infections, acute pharyngitis, or tonsillitis should be treated not only for

the indicated condition, but during this period it is also most advisable to discontinue or reduce Mesantoin medication. With patients requiring a cautious approach it is best to continue the old medication, if any, and begin Mesantoin therapy at ½ tablet daily for one week. This dose can be increased at weekly intervals by ½ tablet daily until an adequate dosage level is reached. As the amount of Mesantoin increases the old medication can be gradually reduced and finally discontinued.

Other observations: In this series of 224 patients, 15 patients became pregnant and continued taking the drug during their pregnancies without any ill effects. They were delivered of sound infants with no side reactions having occurred in either the mothers or their newborn. Several patients from this study suffered from various disorders such as colds, grippe, pneumonia, fractures, surgical treatment for hernia and appendicitis. In not one of these cases was Mesantoin therapy interrupted except in those patients having acute infections.

Mesantoin is a valuable adjunct to the existing list of antiepileptic preparations. Grand mal seizures can be adequately and satisfactorily controlled. A careful therapeutic regimen must be followed and, in addition, care must be taken to adjust dosage for each individual patient, so that untoward reactions can be kept to a minimum.

SUMMARY AND CONCLUSIONS

1. A careful review of the literature reveals that sensitive individuals can react severely to Mesantoin therapy. For this reason, a program is outlined which will be helpful in keeping side reactions at a minimum. (a) Patients with past histories of allergy or drug sensitivity should be treated with caution. (b) Patients requiring large doses (0.8 Gm. or more) should be watched carefully. (c) The drug must be discontinued immediately if rash, abnormal vaginal bleeding or bleeding from the gums occurs. (d) Careful investigation and reduction of Mesantoin if pruritus, lacrymation, "canker sores," or postauricular exfoliation occurs.

2. Side effects reported in this study: 16 per cent complained of drowsiness which could be controlled with Benzedrine in severe cases; 9 per cent developed a rash; 5.5 per cent developed a mild pancytopenia, not requiring discontinuance of the drug; one patient developed moderate pancytopenia requiring careful observation.

3. A series of 224 patients are reported in which a 50 per cent reduction in expected grand mal seizures was obtained as compared to previous medication.

4. Of these patients, 182 or 81 per cent derived definite benefits.

5. Dosage procedure is described whereby Mesantoin is substituted equally for previous medication.

6. When properly administered, Mesantoin is an effective and safe drug for the control of grand mal epilepsy in view of the results obtained in this seven year clinical study.

I am indebted to Drs. David J. Impastato and J. J. Guttman for many valuable suggestions and constructive criticisms. I also wish to thank Dr. B. L. Pacella for the electroencephalographic studies.

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Role of Food Allergy in Multiple Sclerosis

Otto F. Ehrentheil, M.D., Maurice H. Schulman, M.D. and Leo Alexander, M.D.

THE role of allergy and particularly food allergy in the etiology and pathology of multiple sclerosis has been discussed for many years. A very extensive literature has developed on this subject and was reviewed by Ferraro[1] in 1944, by Reese[2] in 1946 and by Abramson[3] in 1948. There are seven major findings of different authors which when assembled suggest a relationship between multiple sclerosis and food allergy.

1. Vascular changes have long been recognized in allergic reactions.[4–7] The pathologic anatomic findings in multiple sclerosis show changes in the blood vessels and blood supply of the central nervous system.[8–11] Ferraro[1] reported a marked analogy between the pathology of experimental cerebral anaphylaxis and demyelinating disease. We wish to draw here only the conclusion that the pathologic findings in multiple sclerosis are not inconsistent with an allergic tissue reaction.

2. The clinical course of multiple sclerosis with its periods of acute exacerbations and remissions is quite similar to the clinical course of many allergic diseases. Kennedy[12] has stated that the pathologic findings and clinical course of multiple sclerosis might conceivably be produced by multiple localized, edematous, cerebral allergic reactions.

3. Many workers have produced multiple sclerosis-like lesions in animals by eliciting an allergic reaction in the brain tissue.[1, 13–15]

4. The importance of nutrition in multiple sclerosis has been described by several authors. Dattner suspected a relationship between nutrition and multiple sclerosis.[16] Probably influenced by the then recently discovered liver therapy for pernicious anemia and combined system disease, he postulated a similar mechanism in the genesis of multiple sclerosis. He described among others a case which seems so relevant to the present discussion that he is quoted directly:

From the neurobiologic unit and the multiple sclerosis research clinic, Boston State Hospital.

Supported by a grant from the Massachusetts chapter of the National Multiple Sclerosis Society.

"The first case concerns a 36 year old female patient who has been under my observation for five years. She developed multiple sclerosis when she was 19 years of age and had several subsequent attacks of retrobulbar neuritis, paresis of extremities, dizzy spells with cerebellar-atactic signs, and paresthesias in different areas. Six of these attacks were manifested by disturbances of the optic nerve and occurred after eating fish, lobster, caviar, anchovy, and fish mayonnaise. These attacks caused the patient to be almost blind but she always recovered with only small remaining lesions . . ."

Dattner assumes in this case an avitaminosis. From the allergic point of view it is most impressive that each attack was reportedly antedated by the ingestion of seafood.

Brickner and Brill observed that a large majority of multiple sclerosis patients were either food faddists or poor eaters; in particular the intake of fats was found to be small.[17] Shields hypothesized a relationship between the use of commercial fertilizer and multiple sclerosis.[18] It was his opinion that even animals fed crops from a soil treated with artificial fertilizer lacked the "trace elements" and perhaps some unknown factors. This line of reasoning led him to the deduction that the Chinese, who use human excreta as fertilizer, are free of multiple sclerosis, arteriosclerosis and hypertension for this reason.

However, there are many difference in the way of life of the East and West other than the use of human and animal excreta as fertilizer. In China milk and milk products are not a part of the normal daily diet, and rice is the preponderant cereal in the diet.

The problem of the importance of dietary variations was raised by Alexander who reported no new cases of multiple sclerosis in United States Air Force personnel stationed in a certain area in England.[19] In a similar British base in the same area new cases of multiple sclerosis occurred among British personnel with the same frequency as in the British civilian population. The living conditions, the type of barracks, the climate and to a great extent the food were identical at both bases, with one exception: the United States soldiers were supplied with evaporated or dried milk while the British soldiers were supplied with fresh milk from local sources. This finding caused Alexander to reason that multiple sclerosis might be caused by a virus contained in fresh cow's milk but killed in the manufacture of evaporated milk. Though the virus theory and the contraction of the disease from fresh cow's milk may still hold true, it should be pointed out that the allergen of milk is also greatly reduced in the process of evaporation.

5. Many authors have observed allergic reactions in the human brain. Among the earliest to make this observation were Laroche et al in 1914.[20] The textbook of allergy by Urbach and Gottlieb, gives a review of the articles in the chapter of "Allergic Diseases of the Nervous System."[21] More recently Davison has reported cases of food allergy showing paresthesias, muscular twitching, jerking, weakness, paralysis, faintness, partial or total loss of consciousness with or without convulsions.[22] A neurologist reading the list of symptoms and signs in Davison's paper might wonder if some of these patients

might not finally develop typical signs of multiple sclerosis.

6. Kennedy was the first to present case histories suggesting that food allergens might be causative in the development of multiple sclerosis or a multiple sclerosis-like syndrome.[12] Frantz,[23] Squier,[24] and others were impressed by cases which clinically suggested a connection between food allergy and the onset of multiple sclerosis.

7. Baer and Sulzberger tried to determine the role of allergy in multiple sclerosis by clinical investigation.[25] They tested 40 multiple sclerosis patients by the scratch method with 100 different allergens, and allergic histories were taken from 30 of these patients. The incidence of atopic sensitivity found in the group studied was slightly greater than that which occurs in the population at large. Of the 30 patients whose family history was obtained, 10 gave a personal or family history of atopic disease or positive skin reactions by skin tests, or both. The authors concluded that the results obtained in this group did not demonstrate a significant increase over the normal incidence of atopy.

Horton and his co-workers in introducing intravenous histamine treatment of multiple sclerosis did so in an attempt to dilate the cerebral blood vessels.[26] Some authors, e.g., Jonez[27] considered this procedure as a treatment of an allergic condition. Abramson,[3] however, states that the histamine effect depends upon the maintenance of vasodilation by its pharmacologic reaction and not upon desensitization to histamine.

The work of Ferraro[1] and a more recent paper of Rosenow[28] describes the allergic reaction in the brain produced directly or indirectly by infectious processes. Ferraro specifically states that dietary and metabolic studies in cases of demyelinating diseases may lead to the finding of additional etiologic factors along the lines of allergic reactions.

Jonez has also made an allergic study of multiple sclerosis patients.[27,29] He reports on the effect of d-tubo-curarine and histamine together with dietary management of 40 cases of multiple sclerosis, and states, "All patients are tested for their sensitivity to foods, epidermals, molds, fungi, pollens and miscellaneous allergens. The proper diets from an allergy standpoint are prescribed and they are given an allergic extract. The extracts are made using histamine diphosphate in normal saline, 275 mgm. per cc. as a base." Jonez reports an incidence of allergy in 35 of the 40 cases and food allergy in 20 of these, stating, "Our entire study was based on the theory that allergy is the etiological cause of multiple sclerosis. Therefore, our patients are given histamine diphosphate intravenously to the point of tolerance." He also reports results with histamine iontophoresis in addition to d-tubo-curarine and an allergen-free diet. In a table dealing with 62 patients he mentions 46 as having some form of allergy; 22 of these are allergic to foods (either alone or combined with other allergies). The methods employed to determine these allergies were skin testing, history, and occasionally Rowe's elimination diets.[30] The determination of a proper allergic diet was based on the outcome of these tests.

NEW METHODS OF INVESTIGATION

Skin tests have been found unreliable in the determination of food sensitivity.[30–32]. Rinkel found that the diagnostic error of negative skin reactions with food allergens was 29.1 per cent, and the diagnostic error of positive skin reactions of this type was 73.5 per cent. These findings led him to conclude that there is little reason to believe that the occurrence of food sensitivity is in any way directly related to any type of skin response to food extracts. The early work of Baer and Sulzberger[25] and most of the work of Jonez[27,29] are based on the outcome of skin tests.

In recent years three methods other than skin reactions have been developed for the investigation of food sensitivity. The first and most widely known is the elimination diet of Rowe,[30] which is difficult and time-consuming. In multiple sclerosis with its spontaneous remissions and its share of irreversible cerebral changes this method is not feasible.

Another procedure in the diagnosis of specific food sensitivity is the "individual food test" as described by Rinkel[33] and Randolph.[34] However, since multiple sclerosis patients as a group have a marked psychological overlay and are known to be highly suggestible, it was decided not to use the direct-feeding test.

The third method for the determination of food sensitivity is the procedure of ophthalmic testing with food allergens developed by Shulman, who found that the ophthalmic reactions were clinically significant in 85 per cent of the cases tested.[35] This result far surpasses in clinical significance that of skin tests in food allergy. It was therefore decided to employ this method of testing in the present study.

This study was undertaken in an effort to obtain answers to the following questions:

1. How often does food allergy occur in patients with multiple sclerosis?
2. Which foods are most commonly involved in the sensitivity of the multiple sclerosis patient?
3. Do multiple sclerosis patients benefit when placed on a diet from which all reacting foods have been eliminated?
4. Does re-introduction of the eliminated food produce any reaction?

TECHNIQUE OF THE STUDY

A group of 65 clinically proved cases of multiple sclerosis were sufficiently ambulatory so that they could easily come or be brought to the clinic. Two bedridden patients were also included in this study. The ages of the patients ranged from 18 to 56 years. There were 19 males and 46 females. Sixty-one patients had had the disease more than two years when this study was started. Four were recent cases of less than two year's duration.

The following routine was adopted: 1.) A thorough allergic history on a standardized form. 2.) A complete dietary analysis of each patient's food intake on a standardized form. 3.) An examination of each patient's nasal

TABLE 1

DIETS PRIOR TO TREATMENT

No.	Cho	Protein	Fat	Calories	Calcium	Iron	Vit. A	Thiamine	Riboflavin	Niacin	Vit. C	Deficiency due to lack of
1.	I	B	?	?	S	I	S	I	S	I	I	
2.	S	S	S	S	S	S	S	S	S	S	S	
3.	B	S	?	?	S	S	S	S	S	S	S	
4.	S	S	S	S	S	I	S	B	S	S	S	Liver, whole grains
5.	S	I	?	?	I	I	S	B	I	S	A	Milk, eggs, cheese
6.	B	I	I	I	I	I	S	I	I	S	S	Eggs, milk, liver, whole grains
7.	S	I	S	S	L	I	B	I	I	I	B	Milk, eggs, meat, whole grains, fruit, veg.
8.	S	S	S	S	S	S	S	S	S	S	S	
9.	S	S	S	S	I	S	S	S	B	S	I	Milk, citrus fruit
10.	S	S	S	S	I	B	S	S	B	S	S	Milk, eggs, liver
11.	S	S	S	S	I	S	S	S	S	S	S	Milk
12.	S	S	I	B	I	S	A	S	S	S	E	Milk, butter, cream
13.	S	S	S	S	S	I	S	S	S	S	S	Liver, eggs
14.	S	B	S	S	L	B	S	S	I	S	E	Milk, eggs, liver
15.	S	I	S	S	I	I	B	I	I	I	S	Milk, eggs, meat, liver, veg., fruit
16.	S	I	I	I	I	I	S	B	I	S	S	Milk, eggs, butter, liver
17.	S	S	S	S	S	S	I	S	S	S	I	Fruits, citrus fruit, green veg.
18.	B	I	I	I	S	I	S	S	B	I	S	Eggs, meat, liver, fruit
19.	I	I	I	I	I	I	I	I	I	I	I	
20.	S	I	S	S	I	S	S	S	I	I	S	Milk, eggs, meat
21.	S	S	S	S	S	S	S	S	S	S	I	Citrus fruit
22.	S	A	S	S	S	S	I	S	S	E	S	Butter, green veg.
23.	S	S	S	S	I	S	S	S	B	S	S	Milk
24.	S	S	I	B	L	I	I	B	I	S	I	Milk, eggs, meat, liver, fruit, citrus fruit
25.	B	S	S	B	S	I	S	B	S	S	S	Liver, whole grain
26.	S	S	S	S	S	A	S	S	A	A	I	Citrus fruit
27.	S	S	S	S	S	I	S	S	S	S	S	Liver, eggs
28.	S	S	S	S	L	S	S	B	I	S	A	Milk, eggs
29.	B	B	S	B	S	I	S	I	S	I	S	Eggs, whole grains, fruit
30.	S	S	S	S	S	I	S	S	S	B	S	Liver, potato
31.	S	S	S	S	S	S	S	S	S	S	A	
32.	S	I	B	B	I	I	I	I	I	I	L	Milk, meat, liver, fruits, citrus, veg.
33.	S	S	S	S	S	S	S	S	S	S	E	
34.	S	S	S	S	L	B	S	B	I	A	S	Milk, liver, whole grains
35.	S	A	A	A	E	S	S	S	E	S	E	(Milk excess)
36.	S	A	S	S	E	S	S	S	E	S	A	
37.	S	I	I	I	I	I	I	I	I	I	I	Milk, eggs, meat, whole grains, fruit, butter
38.	S	B	S	S	I	I	I	B	I	I	I	Milk, eggs, butter, liver, whole grains, citrus fruit
39.	I	I	B	I	S	B	S	I	A	I	S	Eggs, liver, whole grains, fruit
40.	I	B	B	I	I	S	B	I	I	B	B	Milk, eggs, butter, whole grains citrus fruit
41.	S	S	S	S	S	S	A	B	S	S	L	Fruit, citrus fruit
42.	S	I	I	I	I	I	I	I	I	I	I	Milk, eggs, meat, veg. (green), fruit
43.	B	S	I	B	I	I	S	I	I	I	I	Milk, eggs, meat, whole grains, fruit, veg.
44.	S	L	I	I	I	I	S	I	I	L	L	Milk, eggs, meat, whole grains, fruit, veg.
45.	S	S	S	S	S	S	A	S	S	S	S	
46.	S	S	S	S	I	S	B	I	I	S	I	Milk, fruit, veg.-green
47.	S	I	S	S	I	S	S	B	I	S	I	Milk, eggs, whole grains, citrus fruit
48.	S	I	I	I	S	I	E	I	S	I	S	Eggs, meat, whole grains, fruit, veg.
49.	S	B	S	S	B	S	S	B	B	B	A	Eggs, whole grains, veg.
*	4	14	11	10	25	22	8	15	20	15	16	**Total number of frank deficiencies.*
*	10	21	14	16	26	26	12	26	25	18	18	**Total number of frank & borderline deficiencies.*

Code: L—extreme lack of the food element
I—insufficient intake of the food element
B—borderline intake of the food element
S—satisfactory intake of the food element
A—abundant intake of the food element
E—excessive intake of the food element

mucous membrane. 4.) Skin testing by the scratch method with 15 common foods, plus mixed tree, mixed grass, and ragweed pollens extracts. 5.) Ophthalmic food tests with 25 common foods. In this method the food proteins are incorporated into a bland ophthalmic ointment. A small amount of ointment was placed on the conjunctiva of the lower lid and allowed to dissolve. A positive ophthalmic reaction was characterized by hyperemia in one to four hours. Although these reactions were often accompanied by itchiness, edema of the eye lid, burning sensation, mucopurulent discharge and stickiness of the eyelids some hours later, hyperemia was the most important sign. The sensation of a foreign body in the first few minutes after insertion was disregarded. All patients were kept under observation for about ten minutes after the test in order to guard against a marked immediate reaction, which can be controlled by the ophthalmic instillation of a few drops of adrenaline. Each patient was given a card on which was to be recorded the events following the test at 4, 8, 12, and 24 hour intervals. From the information obtained from these cards and by direct questioning of the patient at the next visit, the result of the test was determined. When no change occurred in the conjunctiva, the test was read as negative. Doubtful tests were called ± but were considered negative after having been repeated with the same result. The allergens employed were not known to the patient. As many as 13 visits at weekly or semiweekly intervals were required for the completion of the whole series, but more were necessary if tests had to be repeated. 6.) A control group of 50 normal individuals were eye-tested for the four allergens which had shown the highest incidence of positive reactions in the multiple sclerosis group. 7.) Complete repeated neurologic and psychologic examinations were done on each patient. 8.) Upon the completion of the tests those patients showing positive reactions were referred to our dietitians and placed on a diet eliminating all food which gave positive ophthalmic reactions. In addition, the foods implicated by the history only were also eliminated. 9.) All patients were kept on this elimination diet for at least three months. At the termination of this period each patient was re-examined neurologically. 10.) Occasionally the eliminated foods were re-introduced, and after a short trial period the patient was again re-examined neurologically.

DIET ANALYSIS PRIOR TO ALLERGEN-FREE DIET

The routine diet of 49 clinic patients was analyzed before each patient was put on an allergen-free diet. Since it was not possible to determine the exact weight or amount of foods eaten, only approximate values could be obtained. Each diet was then analyzed to determine the content of carbohydrate, protein, fat, calories, calcium and iron. Vitamin A, thiamin, riboflavin, nicain and vitamin C intake were also determined. The daily intake thus calculated was then compared with the daily dietary allowances recommended by the food and nutrition board of the National Research Council.[36] For the calcium evaluation the lower standard of 0.8 grams was adopted. The results of this analysis are recorded in table 1.

TABLE 2

OPHTHALMIC ALLERGY TESTS IN 65 MULTIPLE SCLEROSIS PATIENTS

No. of Patient	Egg White	Cow's Milk	Wheat	Corn	Rye	Oats	Rice	Chicken	Beef	Pork	Fish	Shrimp	Orange Juice	Apple	Pear	Strawberry	Cocoa	Nuts	Soy Bean	Lettuce	Tomato	Potato	Celery	Cabbage	Onion
1.	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	±	O	O	O
2.	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
3.	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
4.	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
5.	±	O	±	O	O	O	±	O	O	+	O	O	O	±	±	±	±	±	±	O	O	O	/	+	±
6.	O	O	O	+	+	+	O	O	±	O	O	O	O	O	/	O	O	O	O	O	O	±	O	O	O
7.	O	O	O	+	+	+	±	O	±	±	O	O	O	O	O	O	+	O	O	O	O	O	O	±	O
8.	O	O	O	+	+	+	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
9.	O	O	O	+	+	+	+	O	O	O	O	O	O	O	/	O	O	O	O	O	O	O	O	O	O
10.	O	O	O	±	O	O	O	O	O	O	O	O	O	O	±	O	O	O	O	O	O	O	O	O	O
11.	O	O	O	O	±	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
12.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
13.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
14.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
15.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
16.	O	O	O	O	+	±	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
17.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
18.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
19.	+	O	±	O	+	O	±	O	O	O	O	O	O	O	±	+	O	O	±	O	O	O	±	O	O
20.	O	±	O	±	+	O	O	O	±	O	O	±	±	±	O	+	O	±	O	O	O	O	O	O	±
21.	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
22.	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
23.	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
24.	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
25.	±	O	O	O	O	±	O	O	±	±	±	O	O	±	±	+	O	O	O	O	O	O	O	O	O
26.	O	O	±	O	+	O	O	O	O	O	±	±	±	O	O	+	±	O	O	O	O	O	O	O	O
27.	O	O	+	O	+	O	O	O	O	O	±	O	O	O	O	+	O	O	O	O	O	O	O	O	O
28.	O	O	+	O	+	O	O	±	O	O	O	O	O	±	O	+	O	O	O	O	O	O	O	O	O
29.	O	O	+	O	+	±	O	O	O	O	±	O	O	±	O	+	O	O	O	O	O	O	+	+	O
30.	O	O	+	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
31.	O	O	O	O	+	O	O	O	O	O	O	O	+	O	O	+	O	+	O	O	O	O	O	O	+
32.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	+	O	O	O	O	O	O	+
33.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	+	O	O	O	O	O	O	+
34.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	+	O	O	O	O	O	O	+
35.	O	O	O	O	+	O	O	O	±	+	O	O	+	+	O	+	O	+	O	O	+	O	O	O	+
36.	O	O	±	O	+	O	O	O	O	O	+	O	O	±	O	+	±	O	O	O	+	O	±	O	±
37.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
38.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
39.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
40.	O	O	O	O	+	O	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	±
41.	O	O	O	O	+	±	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
42.	O	O	O	O	+	+	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
43.	O	O	O	O	+	+	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
44.	O	O	O	O	+	±	O	O	O	O	O	O	O	O	O	+	O	O	O	O	O	O	O	O	O
45.	±	O	O	O	+	±	O	O	O	O	±	O	±	O	O	+	O	O	O	O	O	O	O	O	O
46.	±	O	±	O	±	O	O	O	O	O	O	O	O	O	O	/	O	O	O	O	O	O	O	O	O
47.	O	O	O	O	+	+	O	O	O	O	O	O	O	O	O	/	O	O	O	O	O	O	O	O	O
48.	O	O	O	O	+	+	O	O	O	O	O	O	O	O	O	/	O	O	O	O	O	O	O	O	O
49.	O	O	O	O	+	+	O	O	O	O	+	O	O	O	O	/	O	O	O	O	O	O	O	O	O
50.	±	O	±	O	+	+	/	O	O	/	+	/	+	/	/	/	O	/	/	/	/	O	+	/	O
51.	±	±	O	+	+	+	/	O	O	O	O	/	±	/	/	/	O	/	/	/	/	O	±	/	+
52.	±	±	+	+	+	+	/	/	O	O	O	/	+	/	/	/	/	/	/	/	/	/	+	/	+
53.	O	±	+	+	+	+	/	/	O	O	O	/	±	/	/	/	/	/	/	/	/	/	+	/	+
54.	O	±	+	+	+	+	/	/	O	O	O	/	±	/	/	/	/	/	/	/	/	/	+	/	+
55.	O	±	+	+	+	+	/	/	O	O	O	/	±	/	/	/	/	/	/	/	/	/	+	/	+
56.	O	±	+	+	+	+	/	/	O	O	O	/	+	/	/	/	O	/	/	/	/	/	+	/	+
57.	O	O	±	O	±	±	O	O	±	O	O	O	+	O	O	/	O	O	O	O	O	±	+	O	+
58.	O	O	+	O	+	+	O	O	O	O	O	O	+	O	O	/	O	O	O	O	O	O	+	O	+
59.	O	O	+	O	+	O	O	O	O	O	O	O	+	O	O	/	O	O	O	O	O	O	+	O	+
60.	/	O	+	O	+	±	O	O	O	O	O	O	+	O	O	/	O	O	O	O	O	O	+	O	+
61.	O	O	+	O	+	±	/	O	O	O	O	/	O	/	/	/	O	/	/	O	O	O	+	/	+
62.	O	O	+	O	+	+	/	O	O	O	O	/	+	O	/	/	O	/	/	O	O	O	+	O	+
63.	O	O	+	O	+	/	/	O	O	O	O	/	O	/	/	/	O	/	/	O	O	O	+	/	+
64.	±	O	+	O	+	/	/	O	O	O	O	/	O	/	/	/	O	/	/	O	O	O	+	O	+
65.	O	O	+	O	+	±	/	O	O	O	O	/	O	/	/	/	O	/	/	O	O	O	+	/	+
A.	65	64	65	65	62	63	63	32	60	64	60	64	54	65	53	52	51	61	53	54	60	65	62	65	54	61
B.	54	1	3	17	4	49	19	1	5	1	3	10	4	10	4	2	4	3	5	4	2	4	5	6	9	11
C.	83.1	1.6	4.6	26.2	6.5	77.8	30.2	1.9	8.3	1.6	5.0	15.6	7.4	15.4	7.5	3.8	7.8	4.9	9.4	7.4	3.3	6.2	8.1	9.2	16.7	18

Any Food	
Egg White	
Cow's Milk	
Wheat	
Corn	
Rye	
Oats	
Rice	
Chicken	
Beef	
Pork	
Fish	
Shrimp	
Orange Juice	
Apple	
Pear	
Strawberry	
Cocoa	
Nuts	
Soy Bean	
Lettuce	
Tomato	
Potato	
Celery	
Cabbage	
Onion	

A: No. of Patients Tested
B: No. of positive Reactions (± Reactions are not counted)
C: % of positive Reactions (±Reactions are disregarded)

O = negative reaction
\+ = positive reaction
± = equivocal reaction
/ = not tested

Eleven of the diets revealed a deficiency in fat intake; 14 were below the recommended level of protein intake; and only four showed a carbohydrate consumption below normal.

A low intake of vitamins in the routine diet was not considered important since all of these patients were taking supplementary vitamin preparations. However, the lack of minerals, especially calcium (in 55.6 per cent of the analyzed diets) and iron (in 48.9 per cent of the analyzed diets), was outstanding.

A similar analysis of the food intake of multiple sclerosis patients was made by Brickner and Brill, who found that multiple sclerosis patients ingested insufficient fats.[17] This finding was present only in a minority of our patients.

FINDINGS BY HISTORY, EXAMINATION OF NASAL MUCOUS MEMBRANES, AND SCRATCH TEST

Among 49 cases of multiple sclerosis, a personal history of allergy was obtained in 14 cases, a family history of allergy in nine additional cases. In some, examination of the patients' nasal mucous membrane showed the characteristics of the allergic membrane but probably with no greater frequency than would be found in the general population. Of the 49 patients who were tested by scratch tests for foods and pollens, twelve (24.5 per cent) showed positive reactions. Four of these had positive reactions only to pollens, two to pollens and food and six to food only. Seven cases who did not show positive skin tests had a personal history of frank allergy. When the cases with a positive personal history are included, the percentage of allergic individuals is found to be 38.8. This is consistent with the findings of Baer and Sulzberger,[25] who found that 33 per cent of patients studied showed evidence of atopic disease.

RESULTS OF EYE TEST STUDIES

The results of the ophthalmic tests are shown in table 2. Incidence of positive reactions is remarkably higher with this method than with scratch tests. Of 65 patients tested, 54 or 83.1 per cent showed at least one positive reaction, 11 or 16.9 per cent of our group did not show any positive reaction.

Reactions to the various food allergens are of interest. Foods which are generally considered highly allergenic such as egg, milk, or cocoa show an incidence of less than 5 per cent of positive reactions while the incidence of positive reactions to the cereals is strikingly high. The highest incidence of positive ophthalmic reactions occurred with rye (77.8 per cent), oats (30.2 per cent) and wheat (26.2 per cent). Only one patient gave a positive reaction with rice extract. Orange, cabbage, fish and onion showed an incidence of positive reactions of approximately 15 per cent each.

The incidence of positive ophthalmic reactions in the multiple sclerosis patients having been determined, a control group was sought. Volunteers from the hospital staff including doctors, doctors' wives, nurses and orderlies of the

same age group and sex distribution were examined. No attempt was made to screen out those with known allergy, since this had not been done with the multiple sclerosis patients. Since all 25 food extracts could not be employed, only those with the highest incidence of positive reaction in the multiple sclerosis group were used, namely, rye, oats, wheat and orange. Two tests were done at one sitting and for the most part only two visits were required.

TABLE 3

POSITIVE OPHTHALMIC ALLERGY TESTS

Food tested:	Wheat	Rye	Oats	Orange
Multiple sclerosis patients	26.2%	77.8%	30.2%	15.4%
Random population—control	8.0%	38.0%	26.0%	14.0%
Allergic patients	40.0%	69.6%	33.3%	44.7%

The results obtained in this control group are shown in table 3, together with results from patients having multiple sclerosis and a group of proved allergic patients.

No parallel exists between skin tests and eye tests. The few cases where both tests were positive could be explained by pure chance. A little less than one-fifth of the multiple sclerosis group did not show any positive ophthalmic or skin reactions. There is of course the possibility that these patients were not tested with sufficient foods, but for practical purpose we must consider these patients free of food allergies. Since these patients unquestionably have multiple sclerosis, it appears that multiple sclerosis can exist without any proved food allergy. Allergic reactions to bacterial toxins were not tested.

ALLERGEN-FREE DIET

To determine whether or not the high incidence of positive eye tests is of clinical significance in multiple sclerosis, the patients with positive reactions were put on an allergen-free diet, and in some instances the allergic food was later re-introduced. In prescribing the diet, the result of the ophthalmic tests was the major determining factor, but also excluded were those foods which according to the patient's history did not agree with him or which he disliked.

Of the 65 patients studied 45 patients were given and remained on allergen-free diets for a period of at least three months. Eleven patients showed no positive ophthalmic reactions; one patient left the city; eight patients did not follow their diets for different reasons.

RESULTS OF ALLERGEN-FREE DIET REGIMEN

After adhering to the allergen-free diet for three months, all patients were neurologically re-evaluated and classified according to the method of Alexander and his co-workers.[37] For the sake of clarity the classification used and their abbreviations are given:

F.R.—full remission without residual neurologic symptoms, with or without minor residual signs.

C.S.R.—clinically significant remission. The complete subjective and functional recovery with some minor pathologic neurologic signs and symptoms remaining.

C.S.I.—clinically significant improvement with lessening of the patient's overall disability but without resulting in clinical or full occupational rehabilitation.

C.I.I.—clinically insignificant improvement with a definite improvement of neurological signs or symptoms without significant lessening of the patient's overall disability status.

N.C.—no change. To this group belong also patients in whom some symptoms improved and some others became worse.

W.—worse, with progression of overall physical and neurological disability.

Full Remission (F.R.): Of 45 patients who followed the prescribed allergen-free diet full remissions occurred in three cases (6.7 per cent). The duration of the illness in these cases was two and one-half years, one month and two years, respectively. One of these was a 23 year old married nurse who had suffered from migraine headaches from childhood until she was 17 years old. She had a history of typical vasomotor rhinitis and marked dermographism. Dietary analysis revealed a daily breakfast of two eggs although she complained of some gastrointestinal distress for several hours after the ingestion of this food. The onset of the multiple sclerosis occurred one hour after eating an egg salad. She developed a large central scotoma of her left eye, and the following day she complained of tingling in her toes and some disturbance of gait. Neurologic examination revealed the scotoma together with greatly diminished and easily exhaustible abdominal reflexes. Allergic study showed positive reaction with egg, wheat and rye allergens. In this patient, who was one of the first in our study, the history and the endermal test were so conclusive that an ophthalmic test for egg sensitivity was not done. One week after start of the elimination diet there was a marked diminution of dermographism, which had existed for many years. Six weeks later she had full remission.

Clinically Significant Remission (C.S.R.): Two patients (4.4 per cent) whose illness had been of six and four years' duration achieved clinically significant remissions. One of these patients had a typical history of numbness of mouth and chin after eating fish. By ophthalmic testing she was also found allergic to strawberries. At one time she inadvertently ate some pastry containing blueberries and developed the same numbness around her mouth. When she avoided all types of berries, this symptom did not recur.

Clinically Significant Improvement (C.S.I.): Clinically significant improvement was observed in nine cases (20 per cent). The duration of the illness in these patients ranged between two and 21 years. One of this group was a 28 year old married woman who had had multiple sclerosis for two and one-half years. She had shown a positive ophthalmic reaction with rye allergen, and when this cereal was avoided her gait improved, optic discs cleared, and muscle strength and reflexes improved. Rye was then re-introduced into her diet, and after four weeks she was unable to use her left leg when climb-

TABLE 4

RESULTS OF ALLERGEN-FREE DIET IN RELATION TO TOTAL DURATION OF DISEASE

	DURATION OF DISEASE				Total Number	Per Cent
	1 year or less	Over 1 year to 3 years	Over 3 years to 6 years	Over 6 years to 33 years		
Total number	1	12	10	22	45	100.0
F.R.	1	2			3	6.7
C.S.R.			1	1	2	4.4
C.S.I.		2	4	3	9	20.0
Total improved	1	4	5	4	14	31.1
C.I.I.		4		6	10	22.2
N.C.		2		7	9	20.0
W.		2	5	5	12	26.7
Total essentially unimproved		8	5	18	31	68.9

ing stairs. Constipation which was relieved with the elimination of rye became troublesome again with its re-introduction. Rye was again eliminated from her diet and after several weeks she was again able to ascend a full flight of stairs. Similar exacerbations upon the re-introduction of suspected foods were observed in 12 instances.

Essentially Unimproved Cases: Ten cases were classified under clinically insignificant improvement (C.I.I.), nine cases showed no change (N.C.) and 12 were considered worse (W). In all, 31 patients of the group studied were essentially unimproved. A 41 year old male exemplified this group very well. In spite of his difficulty in walking after having had multiple sclerosis for 13 years, he was and still is working as a foreman in an electrical appliance factory. In addition to his ataxic gait, his chief complaint was urinary frequency and occasional incontinence. After adhering to his prescribed diet with the elimination of all cereals and fish for three months he was re-examined neurologically and was classified as N.C. He insisted, however, that his urinary difficulty was markedly improved and that he no longer had any nocturia. Four days after the re-introduction of wheat into the diet he again developed urinary urgency, frequency and incontinence, and after one week wheat was again eliminated. Within four days bladder control was restored to its previous level of improvement.

Two other patients had shown marked improvement before starting their diets, and the improvement continued while following the diets. They were therefore re-classified as C.I.I. and N.C. respectively, in spite of doing very well.

Three patients, after being allowed to go off the diet and eat anything, reported that they felt better without the dietary restrictions. One of these patients disliked the trouble of a special diet but admitted having fewer headaches while observing the dietary restrictions.

TABLE 5

RESULT OF ALLERGEN-FREE DIET IN RELATION TO THE TIME ELAPSED SINCE THE LAST PERIOD OF HEALTH OR REMISSION

	DURATION SINCE LAST REMISSION OR ONSET				Total Number
	One year or less	Over 1 year to 3 years	Over 3 years to 6 years	Over 6 years to 33 years	
Total number	13	9	10	13	45
F.R.	3				3
C.S.R.	1		1		2
C.S.I.	2	2	4	1	9
Total improved	6	2	5	1	14
C.I.I.	2	3	2	3	10
N.C.	1	1	1	6	9
W.	4	3	2	3	12
Total essentially unimproved	7	7	5	12	31

EVALUATION OF ALLERGEN-FREE DIET REGIMEN

The results of the allergen-free diet regime are summarized in tables 4 and 5. In table 4 the results are plotted against the duration of the disease; in table 5 the results are plotted against the time-interval elapsed since the last period of remission or full health. As expected, the best results are observed in recent cases or in cases who had only a short period of exacerbation after a good remission.

The evaluation is based on the comparison of the status before and after adhering to the allergen-free diet regimen for three months. A period of three months was considered long enough to achieve results. This proved correct as improvement was apparent in one to six weeks, and none of the patients started to improve after more than three months on the diet.

Whether fewer relapses will occur by rigidly adhering to an allergen-free diet can be evaluated only with a large number of patients and observation over many years. There is the possibility that those patients who did not show improvement during the three-month test period may have fewer relapses in the future while they follow the diet. Such a study is now in progress.

The over-all "success" percentage (31.1 per cent) is lower than the percentage of improvement to be expected spontaneously according to Putnam.[38] The explanation may lie in the fact that most of the patients had long-standing disease. In comparable control groups in the clinic material, similar degrees of significant improvement occurred only in 11 per cent. A medical social worker interviewed clinic patients in order to get a subjective evaluation of the result of allergen-free diets. Of 32 clinic patients who were put on diets, 29 were interviewed. Of these the objective and subjective evaluations were in agreement in 24 cases. There was a difference in five instances. Three patients in this group appeared better subjectively than the objective evaluations, while two patients claimed they were worse subjec-

tively than revealed by the objective (neurologic) examination.

It is interesting to compare the results of the allergen-free diet group with those patients who for any reason were not put on a diet. Three of the patients did not return to the clinic after the testing period. Seventeen patients were treated in the same manner as the above-discussed group of 45 except that they were not placed on dietary restrictions. They also were examined after a three-month period and classified in the same way. Only one of this group was classified under clinically significant improvement (C.S.I.) while the other 16 were in the unimproved group (4 C.I.I., 7 N.C., 5 W).

That the allergen-free regime is helping these patients becomes especially evident when those symptoms are considered which are not necessarily related to, but frequently associated with, multiple sclerosis. Severe headaches were relieved in four cases, nausea after eating in two, constipation in three, diarrhea in two, urinary frequency in five, tiredness in five. Typical allergic manifestations which improved were skin rash in three instances, and vasomotor rhinitis in two.

DISCUSSION

Several results of this study warrant further discussion. The most outstanding finding is the high percentage of positive ophthalmic reactions to rye and wheat in the multiple sclerosis group. Rice, on the other hand, showed a reaction only once. This is especially significant in view of the high incidence of multiple sclerosis in countries where rye bread is most common (e.g. Switzerland), and of the low incidence of multiple sclerosis in countries where rice is the daily food (e.g. China and Japan). The analysis of the routine diet of the 49 clinic patients fits very well into this scheme since a lack of proteins and fats was found much more often than a lack of carbohydrates. A relative preponderance of carbohydrates was noted in the routine diet of multiple sclerosis patients.

The percentage of essential improvement by allergen-free diet in this study of 45 cases may not be striking; however, the group of 17 patients treated similarly to the above group but without dietary restrictions fared much worse. It was impressive that the re-introduction of offending food caused temporary exacerbations in 12 instances. It is also very important in the practical management of multiple sclerosis patients that those symptoms which are frequently associated with multiple sclerosis, such as severe headaches, nausea, constipation, urinary frequency and tiredness, could be alleviated by the diet. The importance of allergic processes in general in the development of multiple sclerosis is consistent with the previously mentioned animal experiments and the pathologic anatomy of multiple sclerosis.

The opinion that food allergy plays a role in multiple sclerosis does not exclude the possibilities of a bacterial allergy, a virus etiology, or of a metabolic disorder. The favorable therapeutic responses to the cereal-free diet may also be partly due to the reduction of the carbohydrate intake; this reduction appears the more significant since the pre-treatment diets of

patients were relatively high in carbohydrates. A disturbance of the carbohydrate metabolism in multiple sclerosis is suggested by the work of Jones who found an excessive amount of pyruvic acid in the blood of his severely ill patients.[39]

The high incidence of positive reactions to rye in the multiple sclerosis group, as well as the smaller though likewise considerable incidence in the random population, raised the question whether or not it may in part have been produced by a nonspecific irritant contained in rye. In investigating this problem it was found that the pH of the rye protein was in the same range as that of the other test substances.

The question also arises whether the so-called "subclinical" allergies found in the general population (according to Vaughan[40] more than 50 per cent of the random population have at least subclinical allergies) may gain relative importance in multiple sclerosis patients because of their vulnerable capillary system. It has been observed often that intercurrent infectious illnesses, trauma, emotional upset or other stress may affect the course of multiple sclerosis adversely. It is possible that allergic reactions may play a similar nonspecific role. It has been found to be good medical management of multiple sclerosis patients to relieve or prevent as much stress as possible. The improvement of the multiple sclerosis patients on allergen-free diet may represent nothing else but an improvement due to the removal of additional allergic stresses.

Clinically a significant improvement was observed within one to six weeks in one-third of those multiple sclerosis patients who were placed on an allergen-free diet. An allergen-free diet regimen based on a carefully taken allergic history and on the outcome of ophthalmic testing is a potentially helpful therapeutic procedure in the management of multiple sclerosis patients.

SUMMARY

1. Ophthalmic tests with 25 different food proteins in patients suffering from multiple sclerosis showed a very high percentage of positive reactions to rye and wheat. This finding proved statistically to be significantly higher than in the random population.

2. Allergen-free diets based on a carefully taken allergic history and on the results of ophthalmic tests brought about favorable therapeutic results in 31 per cent of the cases.

3. In 12 cases the temporary reintroduction of the previously omitted food resulted in temporary exacerbations of symptoms.

4. Symptoms which are not necessarily related but frequently associated with multiple sclerosis, such as constipation, headaches, nausea, general fatigue and urinary frequency, were often alleviated.

5. An analysis of the dietary habits of a representative group of multiple sclerosis patients showed lack in calcium and iron in 50 per cent of the cases, lack in fat in 24 per cent, lack of proteins in 31 per cent, and lack of carbohydrate in only 8.9 per cent.

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Korsakoff's Psychosis Associated With Cerebral Tumors

Bertram E. Sprofkin, M.D. and
Daniel Sciarra, M.D.

THE psychosis to which Korsakoff drew attention includes four prominent features: 1) partial or complete disorientation, 2) confabulation, 3) a retention defect, and 4) a variable degree of amnesia. When a polyneuritis coexists with these mental symptoms, a combination which is more commonly noted in chronic alcoholism, the complete picture of the Korsakoff syndrome is present.

Although the Korsakoff psychosis is a well delineated entity, its etiology is multiple and diverse. Alcohol is responsible for the majority of cases, but this amnestic-confabulatory syndrome has also been noted repeatedly in patients with various central nervous system infections and in such systemic diseases as malaria, typhoid fever, puerperal sepsis and tuberculosis. It has been ascribed to the actions of poisons such as lead, mercury, arsenic and carbon monoxide. Tarachow[1] reported three cases of Korsakoff's psychosis among 105 patients with subarachnoid hemorrhage. This uncommon feature of subarachnoid bleeding is more apt to appear a few weeks after onset of the hemorrhage. Some have attributed the appearance of this mental state under these circumstances to the absorption of toxic products of disintegrated blood, but, as Meadows[2] indicates, "there must be other factors possibly inherent in the individual."

It is this varied etiology of the Korsakoff psychosis that has suggested to some authors, more recently Davidson,[3] that the previous personality pattern of the patient may play a role in the development of this psychosis.

Although the occurrence of mental symptoms in patients with brain tumor is common, Korsakoff psychosis in association with a cerebral neoplasm is unusual. Knapp,[4] reporting upon the mental symptoms of brain tumor, quoted Schuster who studied 775 instances of this condition and tabulated only two cases similar to Korsakoff's psychosis. Grünthal[5] reported this symptom complex in a patient with a craniopharyngioma. In 1941 Benedek and Juba[6] noted

From the department of neurology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute, Presbyterian Hospital, New York.

Read in part at the seventy-sixth annual meeting of the American Neurological Association, Atlantic City, New Jersey, June 18, 1951.

two cases of brain tumor, a craniopharyngioma and a schwannoma, with the classical features of a Korsakoff's psychosis. Lhermitte, Doussinet and Ajuriaguerra[7] described the development of this mental state in a 57 year old man with a tumor of the third ventricle. Caron,[8] in 1946, reported a case of cerebral glioma associated with a Korsakoff syndrome. The patient was a 51 year old man who exhibited diffuse mental and personality changes, seizures and polyneuritis. The patients described by Lhermitte et al.[7] and by Caron[8] had past histories of alcoholism.

During an eight month period three patients with cerebral tumors, studied on the wards of the Neurological Institute of New York, were found to show all of the features of the Korsakoff psychosis. Close questioning of relatives and employers elicited no history of alcoholism in any instance. Two of these patients had proved cerebral gliomas with diffuse midline involvement. The third patient had a tumor in the posterior portion of the third ventricle.

CASE REPORTS

Case 1.—A 53 year old secretary entered the hospital on September 23, 1950. For several weeks prior to admission it had been noted that she was forgetful. About three weeks before hospitalization, because of the belief that every day was Saturday, she stopped working. She became confused and disoriented with respect to time and place but recognized acquaintances. She began to refer to past situations and companions as if they were in the present. Her mood was elevated. For about one week prior to admission she complained mildly of vague headache. No visual or auditory hallucinations were reported. There had been no manic episodes, syncopal attacks or seizures. Her past health was good. There was no history of alcoholism or trauma.

Upon examination, confabulation was prominent and she was grossly disoriented in all spheres. To questions about the date her answers ranged from 1928 to 1947. She insisted that the examiner was someone else whom she had known for many years and spoke of leaving "to get ready for my dinner guests." There was decided impairment of memory for recent and remote events. The remainder of the neurologic examination was not remarkable. There was no papilledema or polyneuritis.

Blood counts, urinalyses and x-ray examinations of the skull and chest were within normal limits. The serologic test for syphilis was negative. A lumbar puncture yielded xanthochromic spinal fluid under normal pressure containing 279 mgs. of protein per 100 ml. and 78 leucocytes per cubic mm., 22 per cent of which were polymorphonuclear cells. A similar increase in cells and protein was noted on two subsequent lumbar punctures. The electroencephalogram revealed ill-defined bifrontal and temporal foci.

Her mental status did not change. She thought she was in a theological seminary, a hotel, and a broadcasting station on various occasions. She greeted staff physicians as old acquaintances and intimates. Although increasing somnolence developed during her second week of hospitalization, repeated examinations disclosed no focal neurologic signs.

Ventriculography on the eighteenth hospital day was indicative of a bilateral tumor of the inferior frontal region extending into the septum pellucidum and corpus callosum. Another significant deformity was abnormal separation of the lateral ventricles in the sagittal projection, the septum pellucidum measuring 2 cms. in width (figure 1). A right frontal craniotomy revealed no gross tumor tissue, but a needle biopsy of the right frontal lobe led to the diagnosis of glioblastoma.

She became negativistic and progressively more lethargic. Her condition deteriorated and she expired on the thirty-second postoperative day.

FIG. 1 (*Case* 1).—Ventriculogram showing abnormal separation of the lateral ventricles.

At autopsy she was found to have a large neoplasm which was roughly central in position in the frontal region. It occupied the septum pellucidum and fornices and extended into the corpus callosum, caudate nuclei and thalami. From these structures it impinged upon the lateral and third ventricles (figure 2). Microscopically, it was a rather cellular highly vascular tumor diffusely invading neural tissue and reaching the ventricular surface at many points. The walls of the third ventricle were infiltrated with neoplastic tissue. Extensive necrosis and a number of pseudopalisades were noted. Occasional binucleated and multinucleated cells were seen. *Histologic diagnosis*: Gliobastoma.

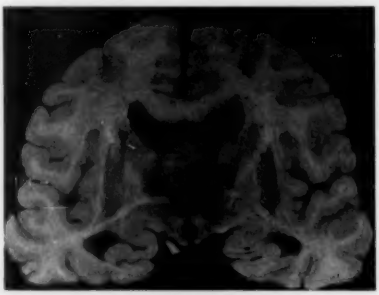


FIG. 2 (*Case* 1).—Photograph of coronal section of the brain showing midline glioma involving septum pellucidum, corpus callosum, caudate nuclei and thalamus.

FIG. 3 (*Case* 2).—Ventriculogram showing filling of only the dilated right lateral ventricle.

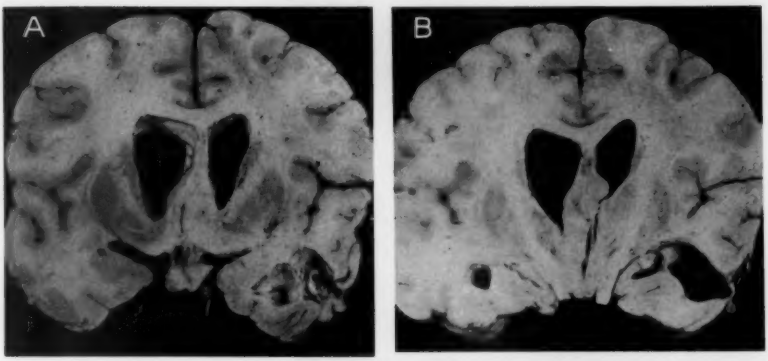
Case 2.—A 62 year old male cashier was admitted to the hospital on February 23, 1951 because of peculiar behavior during the previous ten days. For a period of 35 years he had had generalized convulsive seizures, which were completely controlled by Dilantin for 12 years prior to admission with the exception of one seizure when medication had been temporarily discontinued.

Ten days before hospitalization he began to act negativistic, indifferent and apathetic. A few days later he stopped working. He began to talk irrationally on occasions and complained of fatigue. He was disoriented with respect to time and showed impairment of memory for recent and remote events. He became somnolent two days before admission. No history of alcoholism or trauma was obtained.

Upon neurologic examination it was noted that he was euphoric and facetious. He was disoriented as to time. Memory was decidedly impaired. He did not recognize his family physician. He confabulated freely concerning the length of his hospitalization and other recent events. The examination was otherwise not contributory.

The hemogram, urinalysis, serologic test for syphilis, and x-ray examinations of the skull and chest disclosed no abnormality. A right temporal focus with some extension into the frontal region was noted on electroencephalography. Visual fields were of no diagnostic help because of the patient's inability to cooperate. Lumbar puncture yielded clear, colorless cerebrospinal fluid under normal pressure containing 2 leucocytes per cu. mm. and 30 mgs. of protein per 100 ml. Pneumoencephalography on the tenth hospital day indicated a tumor mass in the left hemisphere in the region of the foramen of Monro. It appeared to block off the left lateral ventricle and compressed the third ventricle, tilting it to the right side. The right lateral ventricle was filled and dilated. The left lateral ventricle did not fill in any projection (figure 3).

In the ensuing days there was a steady progression of mental symptoms with more marked confusion and confabulation. He became incontinent and negativistic. It was thought that both lower extremities and the right upper extremity were weak. Both plantar



FIGS. 4A and 4B *(Case 2.)*—Photographs of coronal sections of the brain showing neoplastic involvement of the midline structures. Infiltration of the optic nerves is evident in A. In both sections the posttraumatic cystic encephalomalacia of the right temporal lobe is apparent.

responses became extensor. The progressive somnolence was followed by stupor. Respiratory difficulty and cyanosis preceded his death which occurred on the thirteenth hospital day.

At autopsy, a large midline infiltrating neoplasm was discovered in the rostrum of the corpus callosum, septum pellucidum and fornices. This extended for varying distances into adjacent structures including the genu of the corpus callosum, the medial walls of the frontal horns of the lateral ventricles, the pre-optic portion of the hypothalamus, and its lateral wall as well as the optic recess, chiasm and nerves (figures 4A and 4B). The third ventricle and both interventricular foramina were directly compressed by the tumor resulting in a moderate internal hydrocephalus. There was herniation of the left temporal lobe into the incisura with compression of the midbrain and the appearance of many recent hemorrhages in this structure as well as in the pons.

In the right temporal lobe there were areas of encephalomalacia with cyst formation. These lesions presented the appearance of old areas of contusion, probably secondary to head trauma during convulsive seizures.

Microscopically, the majority of the tumor cells appeared to be astrocytes and in some places presented the usual stellate form. In most areas the neoplastic elements were slender and elongated. The vascularity of the tumor was low, and there were no areas of necrosis or pseudopalisade formation. On the other hand, the tumor had apparently grown rapidly, contained many cells in mitosis, and showed mild capillary endothelial hyperplasia. This neoplastic process seemed best categorized as a glioblastoma or an astrocytoma which had undergone recent malignant change in the direction of a glioblastoma.

Case 3.—A 41 year old unemployed male entered the hospital on March 18, 1950, and presented a two-week history of occipital headache, nausea and vomiting. His gait was unsteady and wide-based. Speech and coordination were normal. There was rapid, wide amplitude nystagmus on lateral gaze, more marked when he looked to the right. The nasal margin of each optic disc was blurred. The deep reflexes were a trifle more active on the left. No pathologic toe signs were noted.

Blood counts, urinalysis, serologic test for syphilis, and x-ray examination of the skull were not revealing. The electroencephalogram indicated a bilateral frontal focus.

A ventriculogram on the ninth hospital day showed dilatation of the lateral and third ventricles without evident deformity or displacement. Lying within the posterior portion

FIG. 5 (*Case 3*).—*Ventriculogram* showing dilatation of the lateral and third ventricles and a shadow of increased density within the third ventricle.

of the third ventricle and extending slightly more toward the right side was a rounded shadow of increased density measuring about 2 cms. in diameter (figure 5). The radiologist's impression was tumor of the posterior portion of the third ventricle. The ventricular fluid protein was 14 mg. per 100 ml. A suboccipital craniectomy permitted adequate visualization of the cerebellum and floor of the fourth ventricle. These structures appeared normal. A Torkildsen procedure was done connecting to the right lateral ventricle. The patient was then given radiotherapy and discharged on April 28, 1950, after six weeks of hospitalization. Two additional courses of radiotherapy were given subsequently, and he did not re-enter the hospital until March 15, 1951, when he complained of recurrent vomiting for three weeks and was readmitted for further radiotherapy.

He appeared chronically ill and exhibited evidence of considerable weight loss. He was unable to sit or stand without support because of weakness. The suboccipital area of decompression was neither tense nor tender. There was sustained nystagmus in all directions of gaze but not at rest. The rebound phenomenon and hypotonia were noted in the left upper extremity. There was some dyssynergia of the left lower extremity. The deep reflexes were active and equal, and there were no pathologic toe signs. Otherwise there was no change in the neurologic findings.

During the first few weeks after readmission to the hospital it was noted that he was periodically confused and disoriented. He confabulated freely. During one interview he identified the examiner as an old friend, the date as July 25, 1946, and the hospital as a billiard academy. He stated that he had spent the previous day in a lawyer's office and had dined in a restaurant. His memory for recent and remote events was poor. On another occasion he reported that on the preceding day he had witnessed a baseball game between St. Luke's Hospital and the Giants, the latter losing by a score of four to three.

The patency of his Torkildsen tube was established. The ventricular fluid contained about 396 mg. of protein per 100 ml. Air was injected through the tube, and both lateral ventricles were filled, demonstrating the communication between those spaces. They were

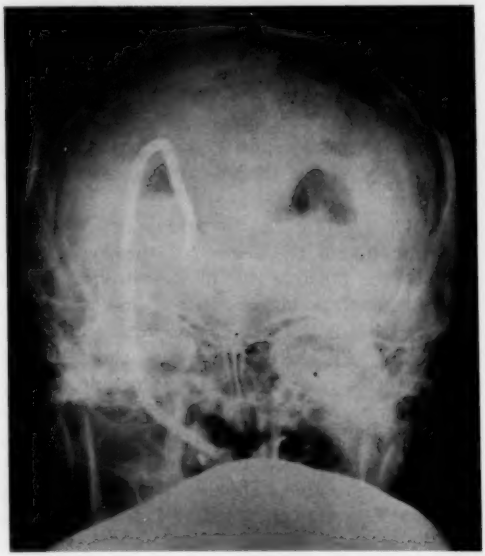


FIG. 6 (*Case 3*).—Ventriculogram, a year after the previous examination (fig. 5) and Torkildsen procedure, showing separation of the lateral ventricles due to midline extension of the neoplasm.

found to be smaller than they were in March 1950 but were separated by 5.5 cm., suggesting extension of the tumor into the septum pellucidum (figure 6). At this time the electroencephalogram was grossly and diffusely abnormal. His condition became temporarily critical and then improved although his mental status showed little change. It was not thought that further surgical treatment was indicated, and the patient was discharged to the care of his physician upon the completion of radiotherapy.

COMMENT

Gamper,[9] in 1928, discussing the pathologic changes in the brains of 16 chronic alcoholics, several having had Wernicke's hemorrhagic polioencephalitis, considered the mammillary bodies as the structure most commonly involved. He quoted Reichardt in whose opinion atrophy of the mammillary bodies constituted the basis of the Korsakoff psychosis. He also cited a case report by Meyer of an encephalitis involving the mammillary bodies in which there was "an outspoken amnestic symptom complex" and a report by Souques, Baruk and Bertrand of an analagous syndrome in a patient with a metastatic tumor of the infundibulum which also involved the mammillary bodies. Grünthal[5] reported a circumscribed destruction of the corpora mammillaria in the case of craniopharyngioma which was mentioned previously. Of the two cases reported by Benedek and Juba,[6] there was complete destruction of the mammillary bodies along with other hypothalamic damage in the patient with the craniopharyngioma. The second patient, who had von Recklinghausen's neurofibromatosis, was found to have a large schwannoma of the third ventricle which compressed the hypothalamus and adjacent structures.

Pötzl, who reported a Korsakoff-like picture as the prominent manifestation of pressure on the anterior thalamus by a cyst, was also cited by Gamper.[9] In a subsequent publication in 1929, Gamper[10] stated that "the brain tumors which so frequently are associated with Korsakoff's psychosis are those expanding lesions which involve the region of the hypothalamus and its neighborhood." Foerster and Gagel[11] noted the Korsakoff psychosis in a patient with a cyst of the third ventricle. The mental symptoms cleared following operation.

It is interesting that the case reports which have been reviewed deal largely with tumors in the region of the hypothalamus and that several authors stressed the possible role of the corpora mammillaria in the pathogenesis of the Korsakoff psychosis. In the first case the mammillary bodies were not involved, but in the second case invasion by neoplastic tissue was noted microscopically. All three cases were characterized by extensive neoplastic involvement of midline structures including those in the neighborhood of the hypothalamus. The widespread invasion by tumor tissue and the associated internal hydrocephalus with involvement of the cerebral hemispheres do not permit of any categorical conclusions concerning an anatomic basis for the Korsakoff psychosis. The one striking similarity between the cases reported here and those in the literature is the midline location of the tumors.

The etiologic significance of previous personality patterns in the development of a Korsakoff psychosis could not be evaluated in the patients presented here. Several authors have stressed the importance of underlying personality traits in the evolution of this mental state. It is suggested that extensive involvement of the deeply situated midline structures along with some underlying personality factor may be the main determinants in the development of a Korsakoff psychosis in patients with brain tumors.

SUMMARY

Three cases of Korsakoff's psychosis have been described in patients with brain tumors. A midline location and extensive involvement were characteristic of all three cases.

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What Has Neurology to Offer Child Guidance?

Arthur R. Timme, M.D.

ALTHOUGH child guidance is concerned primarily with child psychiatry, there are some basic neurologic and neuropathologic considerations which are too frequently overlooked and whose omission leads to much time-consuming and frequently futile psychotherapy. The lessons taught us by the behavior changes which followed the epidemic of encephalitis of 30 years ago appear to have been largely forgotten. Since the virus of encephalitis seems to have a predilection for the basal gray matter, it may be possible to draw a correlation between neuropathology and behavior. The behavior in question, as described by numerous observers, is hyperkinetic, restless, flighty, uncontrolled, impulsive, explosive and frequently over-aggressive and hostile. Proved cases of pathology in the diencephalic area, not only from encephalitis but also following trauma and tumor invasion, have displayed many of these aspects of behavior.

We can safely go a step further. The acute exanthemata of childhood are frequently complicated by encephalitis of varying degrees, sometimes manifest only by hyperpyrexia and delirium, and may leave no permanent reflex, motor or sensory changes. They do, however, produce the behavior described above, again to varying degrees. Most studies have not dealt with these milder states.

Experience with many hundreds of behavior problems arising in the school situation suggests that a postencephalitic core of disturbed behavior lies at the root of the difficulty; this has been unrecognized, frequently resulting in misdirected treatment.

Much of our knowledge of pathologic behavior in children following encephalitis, trauma, diencephalic damage, etc., stems from the work of Bond and his coworkers in this country[1,2] and Hall[3] in England. The element of driven-ness, which underlies the hyperactivity and deficient inhibition, is well described by Kahn.[4]

1930 Wilshire Boulevard, Los Angeles, California.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 13, 1951.

Pathologic localization of the morbid process in these milder forms of encephalitis is naturally difficult and as yet largely speculative. It is generally thought that the virus passes through the cribriform plate and, because of proximity, invades the basal gray matter. There seems to be some affinity for basal nuclear structures, as seen in the frequency of parkinsonian sequelae. But the most convincing evidence is found in the emotional changes (explosive rages, etc.); sleep disturbances (insomnia, reversals, narcoleptic condi-tions); metabolic and growth changes related to the hypophysis and hypothalamus; extrapyramidal motor signs (choreiform restlessness and incoordination); water metabolism disturbances, etc. The work of Cushing and many others has definitely localized most of these functions around the third ventricle, in the hypophysis and adjacent gray matter.

There is a striking similarity between the above changes and those following cerebral trauma, as indicated before. This has been noted by numerous observers. Not many, however, have attempted to localize the actual pathology underlying this group of behavior changes. Friedman[5] has visualized definite organic changes in the encephalogram of head injuries, without attempt at localization. Blau[6] suggests a localized lesion of the prefrontal association area, but does not overlook the actual pathologic "core" which is a disturbed integration or a dissociation between the higher and lower cerebral levels. He further recognizes the importance of the subcortical ganglia in the "system of instinctual drives and motor impulses which form the basis of behavior." Clinical evidence certainly points to a dissociation of the higher and lower levels of cerebral function, and with a striking frequency to the direct involvement of the so-called primitive brain (in both postencephalitic and post-traumatic behavior disturbances) because of accompanying neuro-vegetative and neuro-endocrine symptoms.

Most studies heretofore have not dealt with the milder forms of such disturbances. The absence of immediate and gross neurologic sequelae has apparently caused the investigator of later behavior difficulties to lose sight of the primary insult. Thus Kaiser and Zappers,[7] although they mention headache, confusion, instability and irritability, minimize these in their search for neurologic signs. Healy,[8] in the case of lethargic encephalitis, makes the following points: The severity of the initial infection is not an index of the severity of the sequelae; the age of the onset has no direct relationship to the appearance of symptoms – there may be a long "latency period" up to puberty; there is no correlation between the neurologic signs and the severity of the illness and the effect on intellectual function; the disease is frequently overlooked due to mildness of onset and difficulty of early diagnosis. A careful health history often reveals changes noticeable to the parents in growth, rate of development, self control, emotional response, resistance to fatigue, etc., following one of the infectious diseases or a blow to the head with varying degree of unconsciousness. The age of puberty may later bring out a rapid increase in weight, fainting spells, and increasing sluggishness and disinterest.

The more severe forms of postencephalitic behavior disturbance, like Hall's "Apache" group[3] or Bond's children,[1] are soon recognized as such and constitute a known problem. The underlying mechanism is considered by most observers to be a lifting of the inhibitions exercised by the higher centers over the lower, whether this be a prefrontal lesion, an interruption of certain tracts between the neocephalic and paleocephalic levels (Bonhoeffer[9]), or destruction of some integrating structure. There is an impairment of the physical counterpart of Freud's "censor", or of the controller and regulator of civilized behavior. The clinical picture is a well-defined entity. The milder forms, however, corresponding to Hall's "difficult child"[3] group, may never be recognized for what they really are and may develop into classical orthodox "behavior problems" according to the reactions their behavior calls forth from the environment. A restless, distractible, uncontrolled child meets rejection, repression and severity. He develops rebellion, insecurity and inferiority, and a long train of undesirable compensatory behavior is let loose. Equipped as he is with a poorly integrated nervous system, adjustment becomes increasingly difficult. Almost as destructive to his adjustment are anxiety and over-protection on the part of the parents. Distractibility and scattering of attention lead to difficulty in school; pressure by the parents makes matters worse. Poor muscular coordination prevents adequate competition in play. And so the destructive chain of events might be endlessly prolonged. Although the neural damage of encephalitis was the starting point of the difficulty, it is the interplay of multiple factors that creates the ultimate problem. On the other hand, we have been too easily sidetracked by these later and more visible aspects of the problem; we have overlooked the starting point and thereby neglected some important methods of treatment.

There is a great frequency of pituitary and hypothalamic disturbances in this syndrome. This has both a diagnostic and a therapeutic implication – diagnostic insofar as it tends to localize pathology in the basal gray matter or primitive brain; therapeutic in that it gives clues to aids in treatment. Ten per cent of these children show one or more of the following: disturbances in water metabolism; enuresis or polyuria; increased sugar tolerance with a flat curve; fatigability in the absence of other demonstrable cause; tendency to obesity and Froelich's syndrome; craving for sweets and other carbohydrates; vasomotor disturbances; deficiency of thyroid or gonad function.

What are the specific functions of the human mechanism directly involved, disturbance of which leads to the kind of trouble described above and often finally to delinquency via the path of school maladjustment? These are: (1) disorders of concentration and attention; (2) disorders of emotional control. The importance of power of concentration and of emotional control in the learning process and in group life (school to the youngster) is self evident. Attention and concentration are fundamental to learning; control of the emotions, especially the rage response, is essential to getting along in the group. Most school difficulties relate to disturbance in one or both of these areas.

No one can deny that training is of prime importance in the development of concentration and self control. Successful training, however, depends not only upon proper training experiences, but also upon a reasonable integrity of the nervous mechanisms involved in the habit formation we call training. It is exactly the integrity of these nervous mechanisms that is damaged in the cases upon which this paper is based. Concentrated attention and emotional control require intact cell patterns and connections. It is common experience to find these powers decreased or destroyed after a severe febrile illness or injury. The conclusion is forced upon one that the nervous connections necessary to these functions have been damaged.

The location and extent of these nervous connections and cell patterns are not completely known. All levels of cerebral activity are probably involved. But we have reason to believe that the core of the trouble lies in the diencephalon. Emotion and emotional control are referred to the hypothalamus by numerous writers and researchers; we have only to recall the violent and sham rages of experimental hypothalamic stimulation, of disconnecting the hypothalamus from its cortical connections, or of invading tumors of the third ventricle, in order to see the relationship. Short attention span and distractibility, however, are more difficult to associate with the hypothalamus. Alpers[10] and others describe an "intellectual deficit" in hypothalamic disease, such deficit consisting of loss of memory and inability to concentrate. These are mere differences in degree and modality of the function of awareness, which in turn is related to the function of consciousness-maintenance. Ingham[11] and others support the localization of consciousness-regulation in the hypothalamus. The extreme somnolence or extreme wakefulness in cases of encephalitis are certainly suggestive of such a localization. Probably the acme of activity of this consciousness-maintenance mechanism is seen in the function of highly concentrated attention and the ability to hold it so, shutting out distracting stimuli. Certainly failure of this function leads to a reverse condition of scattered attention at the mercy of any stimulus or to a dropping off into sluggish somnolence.

As to control of the emotions, it is basically human to become angry when things do not go our way. In fact, the behavioristic school declares that the rage-to-thwarting response is one of the three unlearned emotional mechanisms with which a child comes into this world. Normally, growth and training bring this primary emotion under the control necessary to living in a group. Yet there is no doubt that the successful curbing of this primitive instinct requires the integrity of certain neural mechanisms, especially the connections between frontal lobe and hypothalamus. When such connections are severed or the hypothalamus is electrically stimulated in cats, all the physical manifestations accompanying rage ensue—so-called sham rage; when a third ventricle tumor invades the thalamus and hypothalamus, marked automatic unprovoked rage explosions may occur. Rage attacks following insignificant stimuli have also been reported in postencephalitic cases.

While a certain degree of anger and rage is normal, it is excessive irritability or rage out of all proportion in its appropriateness or violence that concerns us here. We see children fly into rages of such extreme that the child is completely inaccessible and uncontrollable, and the attack has to "wear itself out" so to speak, much like an epileptic attack. Indeed, it is felt that there is a relationship to epilepsy in such uncontrollable rages; many of these children show abnormal activity in their electroencephalograms. Thus, in a series of 79 problem cases whose outstanding symptom was temper or rage tantrums with or without adequate stimulus, six showed normal tracings, seven showed what was termed borderline dysrhythmia, and the remainder gave more pronounced findings such as general dysrhythmia, psychomotor waves, a few slow bursts, fast wave bursts, severe dysrhythmia, and some localizing occipital, central and frontal disturbances, mostly dysrhythmia. It is not possible to correlate these findings very exactly with behavior syndrome. They are of course not conclusive, merely suggestive. And it must be noted that dysrhythmia frequently occurs without any clinical cerebral signs.

Thus there are two basic functions essential to the process of adaptation: power of concentration and emotional control. These functions or their anatomic substratum are vulnerable to trauma and infection. Damage to them causes a real handicap to the child, far greater in the long run than many more visible and tangible handicaps. Experience with many school behavior problems, from the kindergarten mischief-maker to the adolescent delinquent, suggests that these functions were damaged early in life in most cases and such damage contributed directly to the behavior problem.

Treatment must be based upon a complete and adequate recognition of the problem dealt with—a poorly functioning or defective adapting mechanism upon which are placed normal expectations. The remedy is obvious. It consists of two parts: (1) information and education of the strategic adults in the picture, chiefly parents and teachers; (2) attempts to repair some of the damage to the mechanism or at least control some of the undesirable manifestations. If the pressures and expectations are reduced as the result of a greater understanding of the child's capacity of performance, e.g., short concentration and attention, over-reaction to thwarting, the first step is taken. Along with this should go attention to the machinery of behavior. Beneficial results have been obtained with long continued administration of small doses of phenobarbital, which seems to reduce the disturbing distractibility and to diminish the ready rage-to-thwarting response which sometimes reaches psychomotor proportions. Concomitant metabolic and endocrine disturbances are treated. It has been found empirically that large doses of whole pituitary substance given orally along with the phenobarbital seem to enhance its effect – just how is not known; it may be by circulatory stimulation of the whole hypophyseal area. In selected cases, Benzedrine sulphate has an astonishing effect in cutting down the driven hyperactivity seen in many of these choreiform children. The psychological effect of regarding and treating these

annoying behavior manifestations as symptoms in a sick child rather than as misdeeds of a naughty child must also not be overlooked.

SUMMARY AND CONCLUSIONS

Many behavior problems have their origin in the childhood infectious diseases, especially when complicated by encephalitis and in cerebral trauma whether during or after birth. The milder degrees of these frequently go unrecognized until the child's behavior brings him into conflict with his environment. As a result of neural damage, these children become hyperkinetic, irritable, distractible, uncontrolled and aggressive. The reaction of adults to this behavior soon creates a problem situation. Besides the history of personality changes after the infection, examination shows choreiform restlessness, poor coordination, hyperactive reflexes and various signs referable to the hypophysis and hypothalamus. Disturbances of sleep and metabolism may be present. These findings indicate that the pathology is localized in the basal gray matter and hypophysis. Medical treatment directed toward autonomic sedation and hypophyseal stimulation may be successful in quieting and stabilizing the child. This eases the surrounding tension and makes subsequent social treatment more efficacious. Childhood infectious diseases should be carefully watched for signs of encephalitis.

Experience with this group of cases emphasizes the need of comprehensive study of every behavior problem from all angles. While it is true that adverse environmental situations call forth undesirable behavior in a given child, it is also true that flaws in the machinery of behavior lead to trouble even in a not too unfavorable environment. These flaws can go unrecognized for years, but can be brought to light through careful history taking and adequate neurologic and endocrine study.

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Treatment Review

Rehabilitation of the Neurologically Disabled Child

A. B. Baker, M.D.

A LARGE number of conditions can and do injure the nervous system of the child with resulting physical, mental and emotional disturbances of varying degrees. The purpose of a rehabilitation program is to treat the child rather than the disease and to obtain the maximum function from the remaining normal nervous system. The handicapped child generally needs special guidance with a program planned and developed around his assets rather than his defects. He cannot escape the realities of daily life with its many prejudices and obstacles, but these can be modified and softened by a healthy, sympathetic environment resulting from intelligently modified contacts with siblings, friends, parents and relatives. If the doctor will devote a little time and effort to instructing the parents as to the nature of the disability and to mobilizing the local resources available for rehabilitation, enough improvement can be achieved to justify the effort and to reward the physician with a grateful, happy child. In milder cases the training program can often be carried out in the home by members of the family with simple improvised equipment, providing they are adequately instructed.

On the basis of our present knowledge, there are three primary divisions in a neurologic training program: 1) evaluation of the patient and his disability; 2) establishment of a treatment goal; and 3) the treatment program.

EVALUATION OF THE PATIENT

In children suffering from damage to the nervous system, the involvement is often not limited to a single area of the brain or spinal cord. Moreover, many associated defects in skeletal development, speech, hearing, vision, intelligence, personality and behavior may be present and must be properly evaluated. The medical examination should determine the patient's general physical status. Deficiencies must all be remedied before adequate rehabilitation can be instituted.

The *neurologic* examination must determine the type, location and severity of the illness and must include an estimation of the expected progress. Since

From the division of neurology, University of Minnesota Medical School, Minneapolis, Minnesota.

Read at the fourth annual meeting of the American Academy of Neurology, Louisville, Kentucky, April 24, 1952.

the success of a training program depends almost entirely upon the nature of the physical disability rather than the actual disease process, the region of the brain involved becomes of utmost importance. These patients must be viewed from a functional point of view and can roughly be classified into the following groups regardless of the actual disease entity implicated: 1) spastic, 2) ataxic, 3) athetotic, 4) rigid, 5) atonic or flaccid. Obviously the ceaseless chaotic movements seen in the athetotic patient will carry a much graver prognosis than the mildly spastic individual. In many cases a mixed clinical picture results.

The extent of involvement naturally varies from case to case and also influences greatly the outlook for retraining. Based on the degree of damage, these patients can be classified as mild, moderate and severe. In some of the milder cases the disability is barely noticeable and little or no rehabilitation is necessary. In other cases, so much damage has occurred that there is complete helplessness. All stages between these occur. In many of the most severe cases there is an associated involvement of the muscles of the mouth, throat and chest producing additional disturbances in speech and swallowing.

Finally, a most important feature of the neurologic evaluation is a determination as to whether the illness is stationary or progressive. Rehabilitation in the face of a progressive and often fatal disease should at best be very limited in its goal. On the other hand, any arrested illness warrants diligent application of training procedures to utilize the patient's remaining assets to the maximum.

The *psychiatric* evaluation should include an appraisal of the patient's basic intelligence and the degree of organic deterioration. There is often very little correlation between the mental and motor involvement in these children. The intellect may be preserved even in the presence of complete physical helplessness, although some children with slight motor impairment show serious deficiencies. Great care must be exerted in evaluating the actual mental status since the association of defects of sight and hearing as well as speech often leads to errors in appraisal of the intelligence. In children of three years of age with mental retardation, rehabilitation becomes extremely difficult. Simple instructions are lost within a few moments and the child is unable to recall the motions that produce desired effects. The outlook in these cases is very poor and is in direct proportion to the organic deterioration.

Finally, the *social evaluation* should briefly assess information concerning the child's home situation and the family's attitude toward the patient and his illness. Often the family situation is not conducive to a normal emotional life. Parental and sibling attitudes are often colored by the presence of the handicapped child. The reaction of the family can be quite varied, sometimes being one of rejection or one of overprotection. Not uncommonly this attitude of overprotection interferes with any opportunities for independent action on the part of the child and keeps him from making progress. Overanxious parents, on the other hand, may push the child too rapidly, demanding a performance at a level equal with that of the normal siblings. The resulting frustration may cause withdrawal and abnormal behavior reactions.

SETTING A GOAL

The second phase of a program of rehabilitation consists of setting a definite treatment goal after considering carefully all factors in the child's medical and social evaluation. All guidance and therapeutic processes instituted by the physician are then directed toward this goal.

The ultimate goal varies greatly from one patient to another. Ideally it is desirable to achieve the following results: 1)) some degree of ambulation, either independently or with some mechanical aid; 2) some degree of self-care activity such as eating, dressing, going to toilet, etc.; 3) some effective means of communication; 4) some degree of social adjustment within the home. For the more severely involved children the ultimate goal may be very limited. This is particularly true of children with severe mental involvement and low intelligence quotients. It is also important to keep in mind the nature of the child's neurologic disability, since the different types of involvements tend to have varying responses to a program of rehabilitation. The *spastic type* is usually the most common and the most favorable to treat while the *athetotic type* is the most difficult to train. In the latter type speech is usually also severely involved. The response of the *ataxic disturbance* will vary with its severity. The milder forms require very little instruction and are often noticeable only as a slight awkwardness or clumsiness during play. Skilled acts such as writing or ball throwing may be difficult. The more severe cases show definite disturbances in equilibrium which may interfere with gait and may respond poorly to treatment. The *atonic type* may be helped considerably through the judicious use of mechanical aids for both self-care and ambulation activities.

It is imperative that the therapy goals which are set should at all times be realistic and within the potentials of the child. The developmental status of the disabled child must be measured in terms of his mental and social development rather than in terms of his chronological age. Instead of seeking ideal results, the physician must be satisfied with practical and functional attainments.

TREATMENT PROGRAM

The final phase of neurologic rehabilitation consists of organizing and guiding the procedures which will help achieve the goal set. The success of such a program does not require a great deal of special equipment. For any of the less complicated cases, rehabilitation procedures can be carried out in the home, providing the doctor understands his goal and is willing to spend a little time with the family and the child in directing the course of therapy. In the more severely involved children, the supplementary services of psychology, physical therapy, occupational therapy, orthopedics and speech therapy may be necessary or imperative.

Before treatment is instituted, the child should be prepared emotionally and psychologically for therapy. Nutrition must be maintained and all physical defects remedied if possible. If the child has a convulsive disorder, this should be controlled with proper drug therapy. Drugs may also be used in an attempt to reduce spasticity and involuntary movements. There is considerable question as to the effectiveness of drugs in this latter case. Orthopedic surgery may be necessary to correct deformities and to stabilize weak or deformed joints. Neurosurgical procedures may help reduce dyskinetic movement. Well-selected braces may be very helpful in preventing contractures, supporting weakened joints, and eliminating extraneous movements.

A detailed discussion of the various treatment procedures cannot be given at this time. At best one can only hope to outline some of the basic treatment principles.

GENERAL TREATMENT PROCEDURES

1. The parts least affected are the best to begin with in introducing the child to treatment procedures. Generally the large proximal muscle groups of

the trunk are more easily controlled and best approached first in therapy.

2. Treatment should proceed slowly at the onset and each treatment session should last but a short interval, not more than 20 minutes twice daily.

3. One should try to get the patient to relax so as to reduce excessive tension and involuntary muscle activity.

4. At the onset of treatment, the child is taught to use separate muscles. The primary muscles for motion of each joint are the first selected for training. This is first done by using passive motion of the relaxed muscle, later followed by active assistive motion.

5. Where muscle weakness is present, the muscles may be strengthened by resistive exercises.

6. In cases where involvement of individual muscles is too great, treatment proceeds immediately to training in composite motor patterns such as balance and walking in the trunk and lower extremities, and grasping, reaching and self-care activities in the upper limbs. In smaller children these composite patterns consist of turning, sitting up, crawling, creeping and standing.

7. As the program progresses, new activities should be introduced as rapidly as they can be learned.

AMBULATION GUIDES

1. The stage at which ambulation begins will depend upon the physical and mental development of the child and the functions already developed at the time of onset of the illness. The simplest motor patterns consist in rolling over, elevating the body and creeping. For the more involved cases, this may be the limit of ambulation.

2. Further ambulation development consists of kneeling, shifting the weight from knee to knee, and finally knee walking.

3. The child is next taught to sit up and to rise to a standing position. While standing he learns to shift his weight from one foot to another. At this stage, the child is ready for ambulation.

4. The patient now progresses through the normal stages of ambulation, first by walking with support and great assistance, and finally by walking alone in the house and then out of doors.

5. Walking accessories are frequently necessary and helpful, particularly if the child can support the weight on his legs and has fair control of his arms. Walking aids are frequently helpful if balance is poor. Full length crutches give the greatest degree of support but carry the danger of axillary pressure. The half length crutch or training stick avoids the danger of axillary pressure but does not give the support of the full length crutch. Canes are the final walking aid before discontinuing walking accessories. Weighted canes may be particularly helpful in giving the child added feeling of security by anchoring the cane to the floor.

In the more severely handicapped, walking aids such as walkers or pushers may be used. The use of railing or parallel bars often enables the child to practice walking without the constant aid of parents or therapist.

SELF-CARE GUIDES

1. In more involved cases, simple maneuvers to develop the use of the upper limbs are most advisable. The use of balls of varying sizes aids in developing such activities as the pushing and rolling movement of the arms and shoulders and the development of the hands by grasping and spreading the fingers. Less involved children can actually develop skilled movements by learning to throw and catch a ball.

2. Eating is a very important self-care function. A three year old child normally has learned to use a cup for drinking and a spoon and fork in eating.

The disabled child may first require passive training with the parents carrying out the entire function for the child. As soon as the pattern is established, active assistance on the part of the child is begun with the parents or therapist guiding the child.

3. Often specially adapted utensils may be required to fit the child's disability. The utensils may be fitted with large handles to facilitate use.

4. Dressing is only developed to a limited extent in a three year old child and such training in the disabled child is often difficult. It is important to give the patient plenty of time to perform any part of this activity and to allow the child to do all he can. The least skilled of the dressing activities is the putting on of outer garments and these should be taught and practiced first.

SPEECH

At three years of age a normal child can usually talk well enough to be understood. However, it is to be expected that the brain-injured child will develop language somewhat more slowly than the normal child. Delayed speech may be due to direct damage to the motor centers resulting in impaired articulation, or to defective hearing, including high frequency hearing losses, to mental retardation, to deprivation of experience, and in rare cases, to aphasic disturbances.

Speech is a function that must be learned, and its training in an afflicted child requires meticulous skillful guidance, usually by a specially trained speech therapist. Competent speech therapy can often spell the difference between success and failure in the rehabilitation program.

Speech therapy with children differs from that with adults. A skillful therapist will use a variety of games, stories, situations, and experiences carefully planned to accomplish selected goals, instead of the techniques that are used with older patients. However, some general principles can be listed.

1. The brain-injured child requires a greatly increased amount of language stimulation. Even more than the normal child, he needs to be read to, told stories, and talked to. Games should be played with him that use language. People should talk to him about things that are happening around him. This principle should be followed by all the people who deal with the child—nurses, physical therapists and occupational therapists, as well as the parents.

2. It is extremely important that parents and other people in the environment should react favorably to the child's speech. Approval should be expressed for any spontaneous speech attempt, whether it is defective or not.

3. An effort should be made to set up situations where the child will want to talk, but pressure should never be exerted to make the child talk or to make him talk differently. The child should never be corrected when he is trying to communicate something.

The goal of speech therapy with these children is to compensate as far as possible for retarding influences, and set up favorable conditions for language growth and development to occur. Direct or indirect pressures on speech, critical attitudes toward the child's speech attempts, and striving for standards which are beyond the child's present ability will impede and not accelerate the acquisition of language facility.

Neurology

Clinical Pathological Conference

From the Veterans Administration Hospital,
Palo Alto, California

Presented by V. E. Gonda, M.D., N. Malamud, M.D.
R. V. Worthington, M.D., N. Burch, M.D.
and Virginia L. Cull, M.D.

PRESENTATION AND CLINICAL DISCUSSION

DR. GONDA: A 53 year old laborer, veteran of World War I, had suffered from grand mal and petit mal seizures and also epileptic "equivalents" since the age of 23. He enlisted in the Army in January 1918 and was honorably discharged in April 1919. The first seizure, witnessed by a physician, occurred in 1920; the same year fellow workmen gave written testimony to the fact that they witnessed the occurrence of convulsions. Following this he had seizures at irregular intervals and of varied intensity. At first several weeks or even months elapsed between attacks, later they averaged at least one a week. It also happened at times that he had several attacks in succession daily. Some attacks comprised merely amnesia for a few minutes; in others the patient fell, had tonic and clonic contractions, foamed at the mouth, bit his tongue and at times split the skin of his scalp open when falling; these lacerations were usually in the occipital region. He vomited after many of the milder attacks; after some severe ones he had involuntary urination and bowel movement. Most of the attacks came during the day, but sometimes they occurred at night. Several times on starting to go to work he wandered away, found himself at home, and went back to work. At different hospitals it was stated that there were some seizures after which, if handled, he would strike out viciously, kicking about and using vile language. Because of this behavior, he had been classified as hysterical. In one hospital where a physician was convinced that he had functional spells only, it was later observed that he suddenly twisted about,

Reviewed in the Veterans Administration and published with the approval of the chief medical director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

looked into space, and within a few moments arose, walked around the room and made ineffective efforts to turn on the drinking fountain with his hand some distance away from the faucet. These movements seemed automatic and lasted about ten minutes. This type of seizure started in 1930 and recurred frequently. The patient also had an aura at times. He was convinced that he had more convulsions whenever he drank even a small amount of alcohol. When he took anticonvulsants regularly he was free from attacks, but when deprived of them he had several seizures a day.

It was first reported in 1930 that after a "dreamy state" the patient began to draw up his right extremities, turning his head and eyes at the same time to the right side, followed by a convulsion of the whole body. Several convulsions localized exclusively to the right side of the body were reported in 1944, but many typical grand mal attacks also occurred in the same year. There was no family history of epilepsy or allied disorders.

After the diagnosis was established, phenobarbital (0.1 Gm. three times a day) was prescribed, to which the same amount of Dilantin was added as soon as that drug came into use.

As in most cases of convulsive disorders, the clinical and laboratory findings, including spinal fluid studies and skull roentgenograms were negative.

It is not unusual to discover that patients give a different history when there is a question of possible compensation than they would give otherwise. This perhaps happened here. After the patient's death it was discovered that when he visited the University of California Clinic in October 1923, he stated that at the age of 12 he sustained a severe accident injuring his skull, following which he had seizures with tongue biting in connection with symptoms characteristic of epilepsy. The notes of the same clinic contain the statement that there were no localizing signs on neurologic examination. During his 15 months of military service there was no record of seizures, and it is important to note that he had not been discharged for medical reasons. Therefore with reasonable certainty we may assume that during this period he was free of seizures. In 1933 he asked for and received compensation for his disability.

In 1944 the patient became argumentative, combative, slept poorly and ate little. The next year he expressed ideas of being poisoned and that his funds were misappropriated. At the same time it was noticed that his speech became slow and drawling at times. Grand mal seizures became less frequent but he had more petit mal seizures. In 1949 he frequently refused medication stating that "phenobarbital will kill a person in a short time." During this year many convulsions were preceded by a period of extreme talkativeness. In the early part of 1950 he became a fairly well adjusted ward patient, but at the end of the same year he again refused to take medicine and developed spells during which he felt he was spinning around.

In January 1951 no seizures were reported, but in February they became frequent. On February 26 five seizures were witnessed in less than two hours; each of these was preceded by generalized restlessness, after which the right frontalis, orbicularis oculi and oris muscles contracted for a very short time and soon convulsed in a clonic manner. The extremities did not participate in the clonic movements excepting the right toes which showed for a few seconds plantar and dorsiflexor excursions. Soon the eyes and the head turned to the right; almost simultaneously the patient's right hand became clenched and the

whole upper extremity extended pointing to the ceiling. The right lower extremity at the same time was flexed in the hip and knee joints so much that the knee approximated the chin of the patient. The attacks lasted less than a minute and were not preceded by vocalization. After they ceased the right nasolabial fold became abolished, and following the third seizure he lost his ability to speak, but in gestures and writing he stated that he was aware of the convulsions. He appeared slightly confused and made some mistakes in his writing. The protruded tongue deviated to the right and profuse salivation developed. An electroencephalogram was carried out at this time. More seizures, both localized and generalized, occurred this same day, and in the same evening the right plantar response and right cremasteric reflex could not be obtained. The attacks, notwithstanding continuous medication, grew more frequent. The stupor deepened, the patient aspirated material from his mouth. On March 1 flaccid paralysis of the right extremities developed. The deep reflexes diminished on the same side but there were no pathologic pyramidal responses. Simultaneous pressure on both facial nerves at the space just behind the parotid gland caused prompt contraction of the left facial muscles, especially visible in the appearance of the nasolabial fold, but none on the right side. During some of the seizures the eyeballs started to wander to the left, then forcefully turned to the right, and the right extremities became spastically extended and the left ones simultaneously flexed.

From all these manifestations it was believed that the responsible lesion was localized in and around area 8 on the left side of the brain. The spells described years ago as focal ones starting after accidental injury to the head warranted the supposition of chronic local damage. On the other hand, the dramatic onset of serial seizures before the death of the patient made us seriously consider some additional factor, most probably some acute vascular accident.

On March 2 the patient responded more to painful stimuli and the right biceps reflex became more lively; the next day slight neck rigidity developed, and Kernig and Brudzinski signs were present. No patellar or achilles reflexes could be obtained, nor pathologic pyramidal responses.

The patient did not respond to treatment. On March 4, 1951, the temperature rose to 106° F. and he expired.

ELECTROENCEPHALIC DISCUSSION

DRS. WORTHINGTON AND BURCH: During the four months preceding the death of this patient, four electroencephalograms were made. The last examination is of particular interest because it was associated directly with seizures occurring during the course of the recording. The case affords an opportunity for close correlation of electroencephalographic data with the results of clinical observation and postmortem findings. Examinations were made on November 16, 1950, December 14, 1950, January 23, 1951, and February 26, 1951.

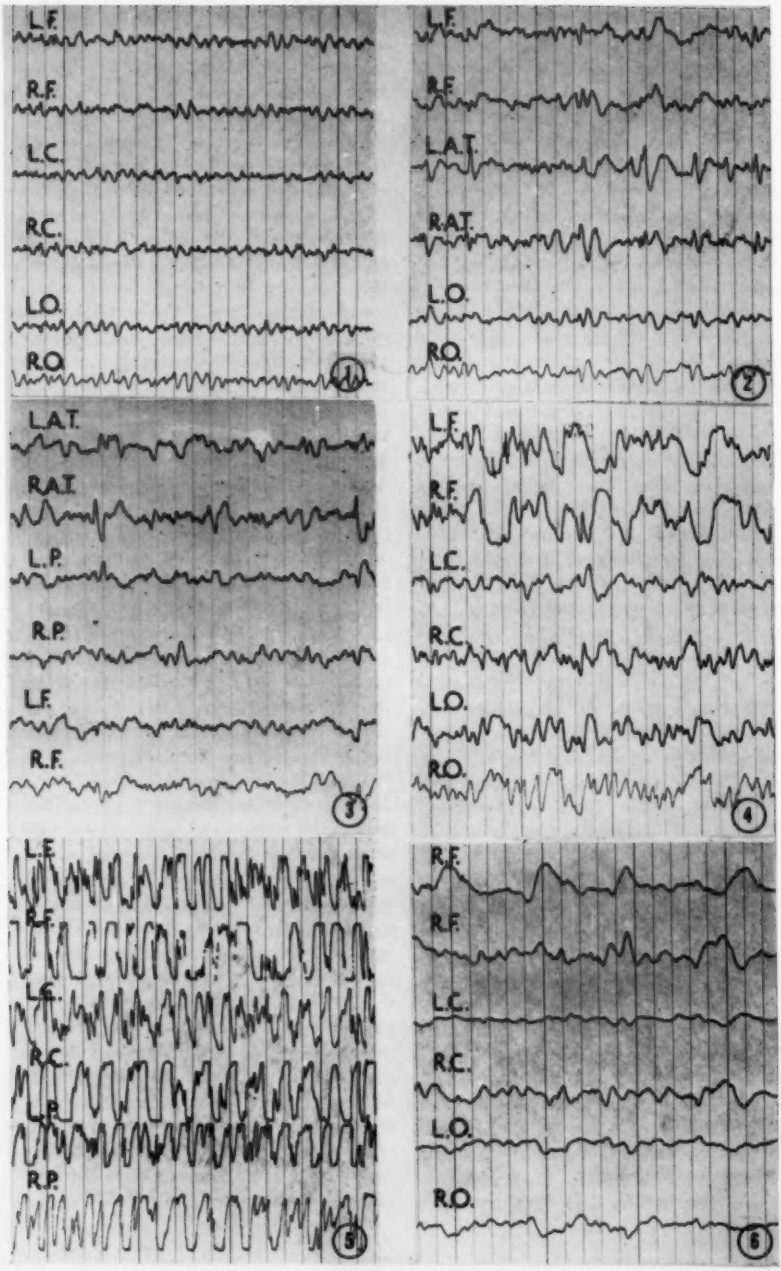
The record of November 16, 1950 shows only the waking state, while the others show waking and sleep. No sedation was used for obtaining sleep. The record showing least dysrhythmia is that of January 23, 1951, and this fact is probably associated with the absence of observed seizures during that month. The most abnormal is that of December 14, 1950. The November record is intermediate. The most normal record, that of January 23, 1951, shows a basic rhythm of irregular moderate voltage 7–8/sec. activity with superimposed and intermixed low voltage 20/sec. (figure 1). The 20/sec. is best seen in the anterior

leads, and sometimes rises to moderate voltage. The left central is slightly flattened as compared with the corresponding right lead and in particular shows a lower voltage and lesser amount of the fast activity. No further evidence of abnormality is seen until the patient falls asleep, and then seizure activity appears in the form of isolated spikes and sharp waves which are sometimes biphasic and sometimes followed by a slow wave or two (figure 2). These are seen most prominently in the anterior temporals on both sides, usually not simultaneously, and can be picked up in lesser amplitude in the ears, temporals and frontals. The sleep spindles can be made out on both slides but are not prominent. In deep sleep some bilaterally synchronous large slow waves occur.

The record of December 14, 1950 shows considerable generalized dysrhythmia. The basic pattern is a very irregular mixture of slow waves ranging from 2/sec. up to 8/sec. At times there is some 8/sec. in the occipitals. The most striking feature is the spike seizure activity which is seen in the anterior temporals, frontals, temporals and ears, having its highest voltage in the right anterior temporal where it also occurs most frequently. These spikes are sometimes bilateral and at other times limited to one side or the other. They frequently take the form of a small, sharp positive deflection, followed immediately by a high voltage negative spike, which in turn is followed by a sharp positive wave. This spike complex may then be followed by a large slow wave. The left parietal appears flattened as compared with the right, especially in high frequency response. Sleep was obtained without sedation, and shows the spike seizure activity of the anterior temporals and the flattening of the left parietal even more clearly (figure 3).

On February 26, 1951, after the onset of the seizures described above, the patient had right-sided attacks intermixed with generalized ones during the examination. The interseizure record prior to the occurrence of the grand mal attacks shows a somewhat irregular moderate to high amplitude 8½/sec. in the occipitals, and a very irregular mixture of slow waves throughout the other leads. These waves range from 2½/sec. to 8/sec., the largest and slowest waves being most marked in the anterior leads particularly the frontals and anterior temporals. The left central shows a reduced amplitude and lack of synchrony as compared with the right central (figure 4), and this asymmetry increases with succeeding seizures. High voltage negative spikes occur particularly in the right anterior temporal, but also occasionally from the left, and are seen simultaneously but not of such high voltage in the frontal, temporal and ear leads of the same side.

The onset of seizures as seen in the record is abrupt with a rapid crescendo of very fast activity which seems to be largely muscle activity in all leads, so that no premonitory changes or localizing evidence can be made out. High voltage 3–4/sec. waves without lateralization become prominent toward the end of the seizure and following the unilateral attacks the record returns without delay to the pre-seizure appearance. The record during the grand mal attacks is essentially the same as the above except for the greater duration and the prominence of high voltage 3–4/sec. (figure 5.) Following the first grand mal, however, the whole appearance of the record is changed. It is flattened out and remains so even when the patient has recovered sufficiently to obey simple commands. The left central lead becomes particularly flattened, and thus stands out as a focus almost deprived of activity (figure 6).


L.F.
R.F.
L.C.
R.C.
L.O.
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1
L.F.
R.F.
L.A.T.
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2
L.A.T.
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L.P.
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3
L.F.
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4
L.F.
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5
R.F.
R.F.
L.C.
R.C.
L.O.
R.O.
6

FIG. 1–6.

All records show abnormality, but the amount varies widely and probably is related to the frequency of occurrence of the seizures. When the record is most abnormal, for example, during repeated seizures and especially after a grand mal, the correct focus is unmistakably shown by flattening and loss of activity over the involved area. When patient's seizures are being controlled and are occurring only infrequently, it becomes increasingly difficult to demonstrate the focus. In the examination of January 23, 1951, the only finding that pointed to the actual focus was a minimal depression of the amount and amplitude of a 20/sec. fast component in the activity of the involved area as compared to the homologous area of the opposite side. This finding was consistently present throughout all recordings but the difference was so small that it might easily be dismissed as insignificant in a routine examination. The depression of activity over the focal area is apparently largely a result of the seizures occurring at the time, rather than a fixed depression of activity such as is associated with some other localized cerebral diseases. It may be regarded as an exhaustion phenomenon, related to the Todd's paralysis and aphasia exhibited following seizures.

The spike seizure activity actually found in all of the examinations was misleading as to the location of the focus. It was found in the anterior temporals and predominantly on the right, i.e., on the opposite side to the actual focus. One may speculate that the scattered spikes appearing on both sides are a measure of the general epileptic tendency of the patient rather than being a focal phenomenon. On the other hand, they may be related to the gliosis found in the cornu Ammonis, but neither of these suggestions explains the relative absence of spikes from the area involved directly in the focal seizures.

The recording of the actual seizures themselves did not contribute any reliable localizing information. The obvious clinical lateralization seen in the seizures was not reflected in the electroencephalogram, probably because of the abrupt onset of muscle and movement artefacts obscuring the true sequence of cerebral activity.

NEUROPATHOLOGIC FINDINGS

DR. MALAMUD: *Macroscopic observations*: The brain weighed 1490 Gm. It was edematous and congested but symmetrical. The basal vessels were delicate and entirely free from atherosclerosis. The leptomeninges were generally thin with the exception of scattered foci of fibrosis. The convolutions were well outlined and not atrophic although some of the sulci were slightly widened. Coronal sections revealed normal outlines of gray and white matter and normal size of ventricles, but a suggestion of atrophy of the right cornu Ammonis. All deep structures including the brain stem and cerebellum appeared normal.

Microscopic observations: Sections from various parts of the brain disclosed the following lesions: 1) sclerosis of the right cornu Ammonis involving the end plate and Sommer's sector which were completely devoid of neurons and were replaced by dense gliosis; 2) diffuse loss of Purkinje cells in the cerebellum; and 3) numerous minute superficial scars limited to the cortex of the left inferior frontal gyrus, particularly the pars triangularis. The latter consisted of wedge-shaped foci devoid of neurons and containing variable amounts of fibrous astrocytes, glial or collagenous fibres and cysts. The lesions either penetrated the cortex from the meninges or were entirely cortical (figures 7 and 8).

While the sclerosis of Ammon's horn and of the cerebellum are common findings in cases of so-called idiopathic epi-

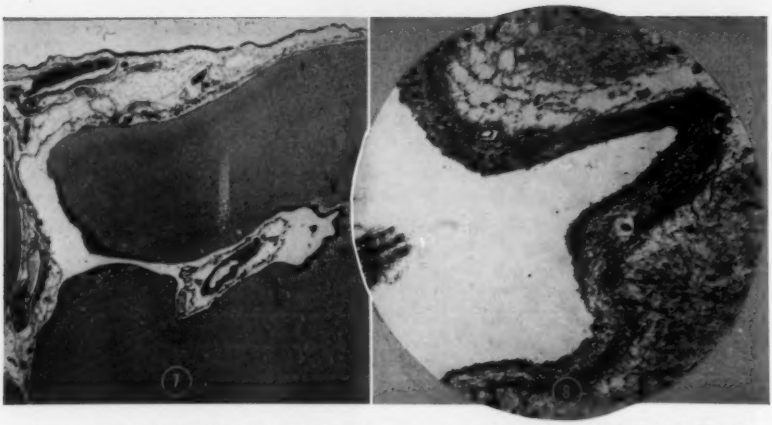

FIG. 7. Section from left inferior frontal gyrus (Broca's area) stained with Holzer's gliafiber method. X marks a focus of glial scarring within the cortex at the junction of the pars triangularis and pars opercularis.
FIG. 8. Magnification of the area marked X in figure 7, showing a cortical cyst lined by glial fibers.

lepsy, the cortical scars and their restriction to Broca's area and neighboring regions are considered significant in view of the type of focal seizures observed in this case. Etiology of the scars remains unknown but trauma is probable.

Dr. Cull, the pathologist of the Veterans Hospital, found bilateral bronchial pneumonia of aspiration type; nephrosis with lower and upper nephron involvement; petechial hemorrhages in the lungs, stomach and pituitary gland which latter was hyperemic and contained a circumscribed adenoma at the base of the anterior lobe; the cells of this adenoma were round, polygonal and possessed moderately eosinophilic cytoplasm with large, often eccentric, sometimes multiple nuclei.

CONCLUSION

DR. GONDA: This case is presented in detail because it is hoped that it may contribute toward more careful evaluation and interpretation of the clinical and electroencephalographic findings with a view to possible surgical removal of the pathologic focus. We are well aware of the difficulties in identifying during surgery the areas to be removed, but important methods which aid in the exact localization of the firing focus are now available. Knowing that where objective lesion of brain can be proved as the causative agent of the seizures, permanent disappearance of seizures practically never occurs, either with or without medication. This should incite us to more radical help even if the pathology is in the "dominant" hemisphere, parts of which may be resected without deleterious effect upon the patient.

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Historical Note

Lasègue Sign

D. T. Dimitrijevic, M.D.

IT IS NOT UNCOMMON in science that a fact transmitted year after year in the texts and literature comes to be accepted as fixed truth. Such an instance is the date of discovery of the Lasègue sign, given as 1864.

Recently Wartenberg[1] pointed out that Lasègue in his famous article "Considérations sur la sciatique" of 1864 made no reference to this sign. It is true that Lasègue used to examine for this sign on his hospital patients, and emphasized its significance to his students. But a careful study of his works fails to reveal any place in which he described it. The first report of the sign appeared in 1881. It was written by Forst, a pupil of Lasègue. This young doctor described it in his thesis, and stated that Lasègue had drawn his attention to it. Forst considered the sign pathognomonic for sciatica and due to pressure on the sciatic nerve. This explanation remained uncontested until 1884, when de Beurmann assumed that it was not pressure but stretching of the sciatic nerve which caused the pain.

However, the straight-leg-raising sign in sciatica (pain on raising the leg extended at the knee) was described before Forst. It was done by Laza K. Lazarevic[2] in 1880. In that year this physician-author published an article which appeared in the Serbian Archives, a publication of the Medical Society of Belgrad. The article is entitled "Ischias postica Cotunnii: A Contribution to its Differential Diagnosis." He described there what is now known as the Lasègue sign. Lazarevic based his observations on six patients with sciatica. He noted the vagueness of the signs and symptoms of sciatica as known at that time, i. e., tenderness of the nerve to pressure, increase of pain on coughing, irradiation of pain, muscle atrophy, hyperhydrosis, vasomotor disturbances. Although these signs and symptoms are often found, they are not characteristic for sciatica. They occur as well in other conditions. Their presence, therefore, is not sufficient to make a differential diagnosis from myalgia, rheumatism, articular diseases and similar conditions Lazarevic's studies led him to the conclusion that the pain in sciatica is not caused by pressure, but by stretching of the nerve. The nerve is stretched most when the knee is extended, the foot dorsiflexed and the leg flexed at the hip. In this position all branches of the sciatic nerve are maximally stretched—as the strings of a violin. The stretched nerves include the posterior cutaneous nerve of the thigh, the common peroneal and the anterior and posterior tibial nerves. In sciatica such

From the Clinic for Psychiatry and Neurology, University of Sarajevo, Sarajevo, Yugoslavia.

a position causes extreme pain. Because any movement which causes stretching of the sciatic nerve is extremely painful, patients avoid all such movements. The most painful point of the stretched sciatic nerve is where it leaves the pelvis.

Lazarevic offered two methods of examination for this stretching test. The first is performed with the patient standing upright. Keeping the knees stretched the patient bends his trunk forward as far as possible without flexing his knees. Sharp sciatic pain results from this maneuver, and often the patient is unable to complete the test. The second test is performed with the patient lying supine. He is either raised to a sitting position, his knees pressed down, or the straight leg is flexed at the hip and moved toward the trunk. In this maneuver the patient feels sharp pain in the buttock.

Lazarevic not only described the straight-leg-raising sign before Forst, but also gave the correct explanation for the resulting pain as being caused by stretching of the nerve. His method of examination included techniques now referred to as "modifications" of the Lasègue sign: a) examination with the foot in dorsiflexion, b) examination with the patient standing upright and bending his trunk without bending his knees.

What Lazarevic said in his Serbian article in 1880[3] he repeated in an article in German in 1884, and still his discovery has remained completely unknown outside of Serbia. It has not been mentioned in any textbook or in the neurologic literature.

If any eponym at all should be attached to the straight-leg-raising sign, it should be that of Lazarevic, since the historical fact remains that he gave the first written report of this sign.

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A distinguished German investigator, Flechsig, has availed himself of the fact that different tracts of nerve-fibres in the brain acquire their white substance at different stages of foetal and infantile life. He has shown, by a remarkable series of investigations, that we may learn as much of the course of fibres by studying them in their birth as in their death – in their development as in their decay. His discoveries have thrown new light on many difficult problems, and supply a trustworthy guide in discovering where the truth lies in other and contradictory descriptions.

–Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

GEORGE BORIS HASSIN, M.D., 1873-1951

George Boris Hassin was born at Elisabethgrad in southern Russia on August 19, 1873 and died in Chicago on August 15, 1951, four days less than 78 years old. Between these dates he lived a story of ambition and achievement so remarkable as to epitomize the American ideal. Out of the harshness of his early struggles and the frequent conflicts with his professional colleagues, he fashioned a pungent and provocative personality which came to be a tradition and will remain a legend in American neurology.

Dr. Hassin was one of ten sons and daughters of a Hebrew school teacher, of whom six became physicians, and three others respectively pharmacist, midwife and dentist. At 23 he graduated in medicine from the University of Kazan, having supported himself by tutoring and caring for a retired army officer with tabes dorsalis, an experience which enlisted his interest in neurology and led him to devote his first studies in neuropathology to tabes. In medical school, Darkschewitz was one of his teachers; another was Wisotsky, with whom he prepared his thesis in experimental pathology—with such resultant aversion to experimental medicine as to constitute a life-long bias.

After graduation he practiced medicine for three years in Siberia 500 miles north of the arctic circle, under the most primitive conditions. But he read scientific journals from Paris, and eventually went to Paris in 1900, and six months later to Vienna, where he associated with such men as Obersteiner, Marburg, Wagner von Jauregg, Krafft-Ebing and Nothnagel. He became intrigued by the thought of going to America, and, less than a year after arriving in Vienna, he landed in New York, going thence to San Francisco. Unhappy there, his restless spirit led him to Leadville, Colorado, a town already well past its zenith, where the ruggedness and crudeness of the life oppressed him. Then Denver attracted him, but he remained there only a month, moving on to Chicago on September 1, 1902 at the age of 29.

His life in Chicago was not easy in the early years, but he remained, abandoning his nostalgic desire to return to Russia. Through thrift and hard work he lived, and through warm sympathy and generosity, easily evident beneath a gruff manner, he held his patients' loyalty. He practiced general medicine at first, but his interests in neurology were strong, and in 1913 he secured a place on the neurologic staff of the Cook County Hospital. In April 1914 he went to Hamburg and worked at neuropathology in Alfons Jakob's laboratory, along with Hermann Josephy and others. The first World War forced his return to the United States where he soon joined the U. S. Army and was assigned to the Army Research Laboratory under Lewis Weed. After the war he returned to his clinical work at the Cook County Hospital where he set up a laboratory of neuropathology. It was in this laboratory and in the one he later headed at the University of Illinois that he exerted his great influence upon such pupils as Percival Bailey, Roy Grinker, Ben W. Lichtenstein and many others.

He taught clinical neurology to the medical students at the University of Illinois from 1920 until his retirement. His were the great days when Hugh Patrick was the leader of Chicago neurology, and Peter Bassoe was one of its brightest lights. He was famous among the students for his sharp wit, his dogmatic opinions, and his biting sarcasm. His trenchant discussions and the Jovian lightning of his condemnation in the medical arena made him famous throughout the land among the profession. Upon a few, in both local and national meetings, fell his unfailing strictures and the heavy-handed bludgeon of his scorn, always with unabashed showmanship. His wit was a Gargantuan club, never a painless rapier. Although he never asked or gave quarter, he often administered his attacks with laughter.

To appraise his life's work requires a frankness equal to his own. As a clinician he was not outstanding, though he impressed the unknowing with his dogmatic assurance. No doubt in his early years he stood in the forefront in clinical skill, but the science of clinical neurology outgrew him as he devoted his

whole life to the microscope. As a neurophysiologist he was unimpressive — sometimes absurd — as in his theories of the "socalled" circulation of the cerebrospinal fluid, drawn from purely histopathologic studies. In the realm of descriptive pathology he was superb, unapproachable, and his textbook is a museum of brilliant photomicrographs. His contributions made the early volumes of the *Archives of Neurology and Psychiatry* indispensable, as they remain. But beyond description he faltered, especially when he ventured into the field of pathogenesis, to which his imagination was unequal. His reading in pathology was encyclopedic, his memory unfailing; he had on the tip of his tongue every important name and reference in his field, which he could quote remorselessly to the discomfiture of either questioning master or pretentious neophyte.

As for the man himself, he alone was the architect of his fate. By magnificent effrontery and indomitable courage in the face of cruel odds, he carved out his own destiny. Though short of stature, he was tall in mind and spirit. By the sheer force of his personality he dominated his scene and silenced his opponents; by the warmth of his feelings he endeared himself to his patients, his friends and his followers. He was at once naive and wise, gentle and harsh. He was generous to the weak and trusting, but confronted the designing with guile, which on occasion overleaped and defeated itself. His students listened with glee, as pretenders fell beneath the pitiless hammer of his ridicule. Devoted to the memory of his Mother Russia, and especially to her music, he espoused American ways and American slang with gusto. Yet his written words wove a pattern of graceful diction as he penned with indelible ink his contributions to American science. He was unique. Fortunate are we who knew and may still recall his rich and piquant personality. We shall not look upon his like again!

ROLAND P. MACKAY, M.D.

To Our Readers and Authors

Very encouraging news has just been received. Starting with the January issue, *Neurology* is to be a monthly publication. We are very proud to have become of age so soon, and are extremely grateful to the publishers for their willingness to accept the responsibility for the added financial burden. They, as well as we, are anxious to have a highly representative journal, and this can be much better accomplished with twelve issues a year.

One of our major problems, up to the present time, has been the necessary delay in the publication of submitted articles. It has been our desire from the beginning that *Neurology* be a medium for the prompt publication of articles dealing with the various aspects of clinical neurology. Unfortunately, with the large number of articles being submitted, together with those read at the annual meetings of the Academy, we have had a little difficulty in accomplishing this. With our expanded publication schedule, long delays will be avoided and the editors will be able to accept a larger number of papers.

A change in the subscription rate will, of course, be necessary with the increased frequency of publication, and the following have been agreed upon by the treasurer of the academy and the publishers: For members of the Academy and other subscribers—$12 per year for twelve issues, as compared to $8 per year for six issues; for junior members—

$9 per year for 12 issues, as compared to $5 per year for six issues. In accordance with a ruling passed at the Louisville meeting of the Academy, members of the Academy are required to subscribe to *Neurology*, and as a consequence, the subscription price to the journal will be incorporated in the membership statements to be sent out in October.

A report covering the first year of publication of *Neurology* was submitted to members of the American Academy of Neurology at its fourth annual meeting in Louisville last April. The accomplishments of the year were mentioned, as well as the problems still before us. Regarding the former, the difficulties of organizing a new periodical have been fairly well overcome; the subscription rate has risen substantially, with readers in all parts of the world; the journal has been awarded a certificate of excellence for the attractiveness of its format and design by the American Institute of Graphic Arts.

It is hoped that with expansion in publication, our journal will continue to grow from an editorial point of view. Our prime objective is to present to members of the Academy, and to others in nuerology and related fields, the most recent advances in research and therapy of diseases of the nervous system. We are planning to expand our section on "Treatment Reviews," and also to initiate a section on pediatric neurology. In addition to these developments, our endeavors for the immediate future will be directed toward greater emphasis on practical clinical material dealing with the diagnosis and treatment of neurologic disease. To accomplish this, we would like to request the presentation of shorter articles, in the dual interest of presenting more material and of keeping the manuscript backlog small enough to allow prompt publication.

We would like to stress to authors the value of brevity in articles. Almost every article written can be shortened considerably without altering its value. In fact, most articles can be improved by being abridged. As stated recently,[1] "Any paper that is fit to be published is written in as good English as the author can muster and then is rewritten at least twice, with a number of words discarded at each writing; for anything that is worth saying at all is usually said twice as well in half the number of words. In its final state it is crystal clear and informative. The references (should be) limited to those of real significance. (The only impression that inflated "bibliographies" make is a bad one.)"

* * *

In accordance with a rotation policy that has been established for all committees of the American Academy of Neurology, of which the Editorial Board of *Neurology* is one, Dr. Augustus S. Rose has been appointed to the board in the place of Dr. Paul F. A. Hoefer. We appreciate the willingness with which Dr. Hoefer has cooperated with us in the early days of our journal, the invaluable contributions he has made, and the impartial judgments he has rendered in making decisions regarding editorial policy.

R.N. DeJ.

Editorial: Jingle Bells, New England J. Med. 245:988, 1951.

Neurology

. . . . . BOOK REVIEWS . . . .

The Diagnosis of Nervous Diseases

James Purves-Stewart, M.D. and C. Worster-Drought, M.D. Tenth edition. 1952. Baltimore: Williams and Wilkins Company. 962 pages. $10.00.

Familiar to generations of medical students, the tenth edition of this work may be considered a memorial, not to say a monument, to its senior author. Like the preceding editions the book is not a textbook in the usual sense, but an exposition of semeiology patterned somewhat on that of Dejerine. Although it does not approach the perfection of that classic, it contains an enormous amount of seasoned clinical information. Used in conjunction with a good textbook of nervous diseases, it should be of great value to any serious student of elementary clinical neurology.

The portions of the book which touch upon anatomy, physiology and pathology are the weakest ones, although they are adequate and generally accurate. But it is in the clinical sections that one feels the vigor and know-how of the accomplished clinical neurologist. In the chapter on Psychoneuroses and Psychoses, for example, the discussions of psychological mechanisms seems superficial and ill-conceived; whereas when the author is on his own ground, adducing clinical examples of hysteria or differentiating the organic from the psychogenic, his writing has the ring of authority. In this edition of the book one notes a marked tempering of the attitude toward psychoanalysis which is treated in several impersonal pages.

The book has been brought abreast of the times by appropriate revisions of many details, notably of the radiological material and that dealing with psychometric testing. A newly written section on electrodiagnosis presents a good brief account of the newer technics of electromyography and of electroencephalography, but fails to make clear what may be expected of these methods and what their limitations are in clinical diagnosis.

As might be expected in a treatise which touches on so many details, there are statements to which exception might be taken. For example: that synaptic transmission of nerve impulses is achieved by the liberation of acetylcholine; that the knee-jerk is not a true stretch reflex; that precocious puberty is the result of destruction of the pineal gland; that tetany is probably due to a toxic disorder of the pallidal cells of the lenticular nucleus; or that the injection of more than 2 ml. of iodized dye for myelography practically commits one to laminectomy. But these are unimportant matters when viewed against the background of the entire work, and do not greatly impair its usefulness.

Mention should be made of the large number (388) of excellent illustrations. The photographs depicting a large variety of clinical states are particularly remarkable, and are reproduced well on good paper. R. B. R.

Surgery of the Peripheral Nerves

Emil Seletz, M.D., (Art Editor, Tom Jones). 1951. Springfield Illinois: Charles C Thomas, Publisher. 185 pages, 136 illustrations. $10.75.

Based upon experience with 2037 nerve wounds, Emil Seletz has written a brief description of the surgery of peripheral nerve injuries. In order, the various nerves of the hand, arm, shoulder, leg, foot and head are discussed under the headings of anatomy, course and distribution, characteristic symptoms of injury at various levels, surgical anatomy and incisions for operative exposure and special surgical procedures such as rerouting the nerve. The author has given considerable thought to the type of skin incision which will give the best functional and cosmetic result; a number of the incisions used are original. His suggestions should be carefully considered by all surgeons repairing peripheral nerves, since improper incisions cause annoying contractions at joints.

The text, which is very concise, is beautifully illustrated by clear photographs and well conceived, artistically drawn sketches of the surgical anatomy and procedures involved in the operative repair of the nerves.

The atlas—for such it is, more than a monograph—presents the author's viewpoint of the diagnosis and treatment of peripheral nerve injuries. In general, most neurosurgeons would agree with the principles of treatment given. No attempt is made to cover the literature—in fact only a few footnote references are found in the book. An adequate index is appended.

This is a beautiful atlas reflecting credit not only upon the author but upon the art editor, Tom Jones, the medical illustrator, Jean McConnell, and the publisher, Charles C Thomas, who has spared no expense to produce an artistic volume. It should be an indispensible book for all surgeons and a ready reference volume for other physicians who occasionally encounter peripheral nerve injuries. A. E. W.

Skull Fractures and Brain Injuries

Harry E. Mock, M.D. 1950. Baltimore: The Williams and Wilkins Company, 806 pages, $13.50.

This monograph presents the viewpoint of a general surgeon who has made head injuries his hobby for the past 40 years. Written for the general practitioner who must occasionally treat the head injured patient, the book emphasizes measures which are within the capabilities of the average physician or surgeon.

Condemning the "do nothing" form of management, the author emphasizes the potential seriousness of all head injuries. Because head injured patients are often in shock he cautions against unnecessary manipulation of the patient for x-rays or special examinations. The use of morphine is condemned. Certain dehydrating agents, he believes, may be used as indicated in some brain injuries. Lumbar puncture and cerebrospinal fluid drainage in his opinion should be done in one-third of skull fractures and one-third of spinal injuries without fracture. Operation should be delayed as long as possible for he believes the longer the operation is postponed the better the chances of the patient. Rarely is operation necessary within the first few hours.

The book gives a practical discussion of the problems encountered in head injuries from a conservative viewpoint, and may be used profitably by every physician who may be called upon to treat head injuries. A. E. W.

Neurology

Oligodendrogliomas Arising From Structures of the Posterior Fossa

Erich G. Krueger, M.D. and George Krupp, M.D.

INTRODUCTION

In 1921 Hortega[1] demonstrated the true nature of oligodendrocytes as a mature glial cell. Bailey[2] was the first to recognize neoplasms composed of these elements and suggested, together with Cushing, the term oligodendroglioma for these tumors. In his analysis of 2023 intracranial tumors in 1932, Cushing[3] stated that, "Oligodendrogliomas occur almost exclusively in the cerebral hemispheres of adults." In a histopathologic review of the first 13 oligodendrogliomas of the Brigham Collection in 1929, Bailey and Bucy[4] found many cells within these tumors which seemed to be intermediate forms between oligodendrocytes and astrocytes as well as astrocytes; yet, the tumors were essentially composed of oligodendroglia. These authors also commented on cerebellar oligodendrogliomas and likewise predicted their occurrence in the spinal cord since oligodendroglia is present in the spinal cord as well as in the brain. In an extensive review of the subject of oligodendroglioma in 1941, Zülch[5] cited four cases[6,7,8] of metastatic oligodendroglioma in the posterior fossa, adding two cases of his own. The occurrence of primary cerebellar oligodendroglioma was rather doubtful in his opinion.

From the neurosurgical and neurological section, Bronx Veterans Administration Hospital, Bronx, New York.
Presented before the New York Society of Neurosurgery, February 20, 1951.
Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

During the past two decades several observations have been published which changed the original concept of the oligodendroglioma as a tumor occurring almost exclusively in the cerebral hemisphere. In 1926, Dickson[9] reported an oligodendroglioma arising from cerebral midline structures and filling the third ventricle in a six year old child. Thomas and Jumentié[10] published another case of an oligodendroglioma similarly originating from the midline. Martin[7] in 1931 divided the oligodendrogliomas into two groups—a *midline type* (three cases), characterized by the absence of calicification, occurring in young individuals, rapidly progressive course and unfavorable response to operative intervention and a *hemispheric type* (16 cases) occurring in adults, slowly growing and frequently calcified. In reviewing the three cases of the midline type cited by Martin, namely those of Dickson,[9] Thomas and Jumentié,[10] as well as case number 3 of Bailey and Bucy,[4] Zülch[5] states that, "The case of Dickson was a spongioblastoma of the optic chiasm, the case of Thomas and Jumentié an ependymoma and the case of Bailey and Bucy an oligodendroglioma arising from the left occipital lobe." However, Zülch accepted Bailey and Bucy's case number 30 880 as a true midline oligodendroglioma and added five cases of midline type observed among his own series of 67 oligodendrogliomas. These six midline tumors occurred with one exception in young individuals below the age of 21 years. Greenfield and Robertson[6] in 1933 were unable to find any distinction between the oligodendroglioma of midline or hemispheric type on the basis of age distribution, frequency of calcification and duration of illness in a limited series of five cases. Löwenberg and Waggoner[11] divided their 21 oligodendrogliomas into four groups: a unilateral hemispheric type, a bilateral type, a ventricular type and a basal ganglia type.

The first instances of primary oligodendroglioma of the spinal cord were reported by Kernohan, Woltman and Adson[12] in 1931. In a recent review of the literature Russell and Bucy[13] collected six cases of spinal oligodendroglioma in addition to a case of their own among a total of 219 intraspinal gliomas published by various groups between 1930 and 1947. According to these figures, oligodendrogliomas comprised 3.2 per cent of the gliomas of the spinal cord. The relative frequency of cerebral oligodendrogliomas is actually within the same range, namely 3.1 per cent among 862 gliomas (Cushing), 3.1 per cent among 2173 gliomas (Zülch[5]), and 4.6 per cent in 784 gliomas (Wolf[14]).

In following the deduction of Bailey and Bucy that oligodendrogliomas should arise from structures other than the cerebral hemispheres, such as the spinal cord, one could reasonably expect the primary occurrence of this neoplasm in neural structures of the posterior fossa. As far back as 1928 van Bogaert and Martin[15] reported an oligodendroglioma arising from the vermis of the cerebellum and a second case of an oligodendroglioma filling the fourth ventricle. Eight other cases of subtentorial oligodendroglioma have since been placed on record.[16–22] In this presentation it is intended to report three addi-

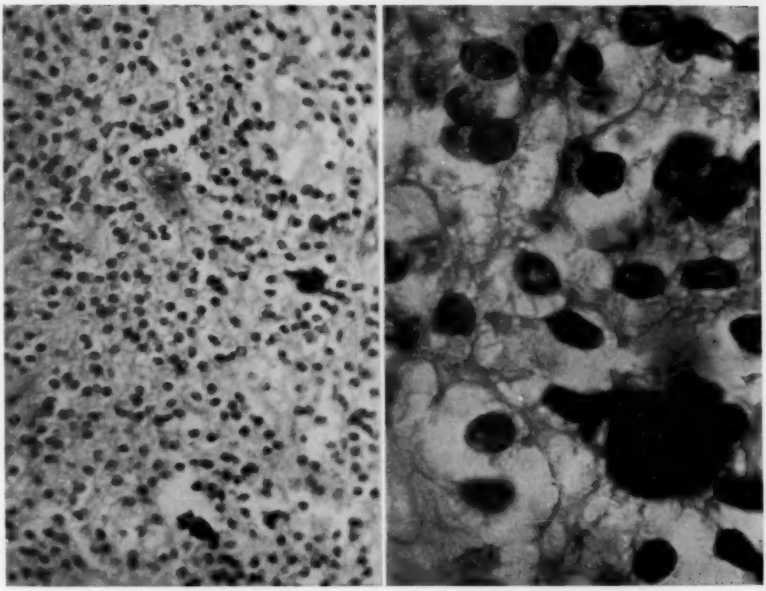

FIG. 1. Photomicrographs of tumor in case 1. (*left*) Showing regularly dispersed small cells with a tendency to form groups and rows. Calcium spherules in upper half of field. Hematoxylin eosin stain x 200. (*right*) Higher magnification showing round and oval nuclei, perinuclear halos and calcium deposit. Hematoxylin eosin stain x 900.

tional cases and to discuss the subject of primary oligodendrogliomas arising from structures of the posterior fossa.

CASE REPORTS

Case 1.—A 20 year old white man gave a history of two posterior fossa operations. At the age of 10 years he had been admitted to a hospital with a six weeks' history of abdominal pain, headaches, nausea, vomiting and drowsiness. During a period of observation he developed an attack of what was described as "hyper-extension" associated with vomiting. On subsequent examinations papilledema, ataxia of the lower extremities and nystagmus were noted. A posterior fossa tumor was suspected and a subsequent craniectomy was carried out. The cerebellar vermis appeared widened and was pinkish-gray in color. A ventricular cannula inserted into the left cerebellar hemisphere struck a cyst measuring 8x7x6 cm., containing clear amber fluid. Two mural nodules were removed. The histologic examination revealed the presence of a calcified oligodendroglioma. The patient recovered and remained symptom-free for about seven and a half years.

At the age of 17, following his enlistment in the U. S. Navy, the patient again developed symptoms pointing to a posterior fossa tumor. Re-exploration revealed a cerebellar midline cyst measuring 3x3 cm. with a tumor mass filling the cyst cavity. A sub-total removal of tumor was done leaving only a small remnant of tumor over the roof of the fourth ventricle. The histologic diagnosis of oligodendroglioma was again made. In May 1943 the patient was discharged from the Navy, resuming his occupation as a factory worker.

During January 1945 the patient again developed headaches, nausea, diplopia and ataxia. A neurosurgical consultant advised against re-exploration and a course of x-ray treatment was given. In spite of temporary improvement the symptoms became progressively worse. On September 23, 1945, the patient was admitted to the neurosurgical section of the Bronx Veterans Administration Hospital.

The patient appeared chronically ill, drowsy, pale and undernourished. He was unable to stand and walk without support. There was bulging in the area of a previous suboccipital craniectomy. There was marked impairment of vision; the pupils were dilated and reacted faintly to light. Papilledema of 3 diopters with retinal hemorrhages was present bilaterally. There was a coarse nystagmus on right and left lateral gaze. Other cranial nerve functions, sensation, reflexes and motor strength were intact. There was marked truncal ataxia with a tendency to fall backwards, but only slight dysmetria in upper extremities. Laboratory studies showed moderate anemia. Roentgenograms of skull showed evidence of previous suboccipital craniectomy. The sella turcica appeared poorly defined. *Diagnosis:* A diagnosis of recurrent cerebellar tumor was made.

Operation: (Sept. 24, 1945) A suboccipital re-exploration was performed through the old midline scar under local Procaine anesthesia. The cerebellar tissue in the midline and also the adjacent parts of either hemisphere appeared pinkish-yellow in color, tough and neoplastic in nature. While taking a biopsy, a small superficial cyst containing clear, amber fluid was entered. An elliptical block excision of the tumor including the roof of the fourth ventricle and overlying tumor was then made. The wound was closed in anatomical layers. *Pathologic diagnosis:* (Dr. Abner Wolf) "This neoplasm is fairly cellular, quite uniform, moderately vascular and contains numerous spherules and plates of calcium of varying size. The tumor cells are small, regularly dispersed with a tendency to form groups or to be arranged in rows (figure 1). The outlines of their bodies are poorly defined but can sometimes be seen irregularly polygonal. The nuclei are small, oval or spherical and relatively deeply stained and uniform. Many of the cells have distinct sharply defined perinuclear halos. *Diagnosis:* Oligodendroglioma."

Postoperative course: The patient made an uneventful recovery and the signs of increased intracranial pressure and cerebellar symptoms subsided. The vision remained markedly impaired with bilateral secondary optic atrophy present. On the last follow-up examination in February 1949 the patient did not show any evidence of recurrent tumor. He married in February 1950. At the time of writing about five and a half years after the last operation, the patient is still alive and well aside from visual impairment.

Case 2.—A 10 year old boy was admitted to the New York Neurological Institute on January 15, 1943. In July 1941 he had had nausea and occasionally vomiting. During March 1942 he developed severe frontal headaches which later shifted to the occiput. In May 1942 a tilt of the head to the right was noted, and during December 1942 the child complained of double vision.

The general physical examination of this thin, white boy was negative except for scoliosis of the thoracic spine and a tilt of the head to the right. There was unsteadiness when walking on a line or when standing with feet together. Papilledema of 2 diopters was present bilaterally. There was nystagmus most pronounced on right lateral gaze. Deep tendon reflexes were active and equal. The neurologic examination was otherwise negative. Laboratory studies were normal. Roentgenograms of the skull were normal except for a questionable separation of the coronal suture. On January 20, 1943, a bilateral suboccipital craniectomy was performed and the fourth ventricle was found to be completely filled by a neoplasm which seemed to arise from the medulla. The tumor was almost completely removed except for a small portion extending into the lateral recess of the ventricle. *Pathologic diagnosis:* (Dr. Abner Wolf) "Oligodendroglioma."

Postoperative course: The patient made a rapid recovery and was ambulatory on the twelfth postoperative day. He was given a course of x-ray therapy and discharged in good condition on February 4, 1943. On May 15, 1943, the patient returned to the Neurological Institute because of thoracic pain and difficulty in walking. It was assumed that he had an implantation of the tumor in his spinal canal, and a complete course of x-ray therapy to the spine was given. Subsequently the patient was transferred to a convalescent home. Here, weakness of his lower extremities became more marked and within the week prior to his last admission he developed paraplegia.

He was readmitted June 22, 1943 for another series of x-ray treatment. The child remained in the hospital for seven weeks during which time his condition became worse, so much so that on several occasions it appeared critical. On August 3, 1943, he was taken home by his parents in a moribund state.

Case 3.—On January 15, 1943, a 22 year old white male was admitted to the New York Neurological Institute with a history of a previous posterior fossa operation. He was first admitted to Bellevue Hospital, New York City, on May 15, 1939, with a history of fronto-occipital headaches of seven months' duration followed later by nausea, vomiting, visual disturbances, veering to the left, tilt of head to the left and attacks of vertigo and tinnitus. Examination revealed 2 diopters papilledema, coarse horizontal nystagmus to the right. Visual acuity was diminished and visual field test showed enlargement of blindspots. Motor power was intact, ataxia absent. The deep tendon reflexes were normal; alternating movements were impaired in the right foot. In June 1939 a suboccipital decompression with excision of a cerebellar tumor was performed. Microscopic diagnosis was "glioma of the cerebellum." He was discharged in July 1939. A few months later all residual signs had disappeared and the patient remained symptom free for two years. In December 1942 the patient gradually developed symptoms pointing to a recurrence of the cerebellar tumor requiring admission to the New York Neurological Institute. The general physical examination was negative. There was an operative bone defect in the suboccipital area. Mild nystagmus and diplopia were present as well as a mild papilledema in both eyes. Visual fields were normal. There was a paresis of the left external rectus and medial rectus muscles. Ataxia, dysmetria and past-pointing of the right arm were noted. Laboratory studies of the blood and urine were normal. The spinal fluid, which was under a pressure of 200 mm. of water, appeared xanthochromic. The cell count revealed 83,000 red blood cells and 533 white blood cells per cu. mm. The spinal fluid protein was 630 mgm. per cent. Roentgenograms showed the operative skull defect.

Operation: On January 26, 1943, a right hemisuboccipital re-exploration was done. The right cerebellar hemisphere appeared ballooned. Transcortical incision revealed a large cyst just lateral to the fourth ventricle. On the lateral wall of the cyst, a mural nodule was found and completely removed. *Pathologic diagnosis:* (Dr. Abner Wolf) "Mixed oligodendroglioma and astrocytoma of the cerebellum." *Postoperative course:* The patient's immediate postoperative course was far from satisfactory, but he finally improved. A course of 12 x-ray treatments was given. On discharge March 19, 1943, the patient walked with extreme difficulty on a broad base. Nystagmus on lateral gaze was present and cerebellar signs in the right upper and lower extremities existed. He also had a right peripheral type facial weakness and blurring of vision. Following discharge, he became progressively worse and finally bedridden. No further follow-up information could be obtained.

DISCUSSION

Table 1 presents a compilation of ten case reports gathered in the literature and of three additional cases of primary oligodendroglioma encountered in the posterior fossa; one of these was a mixed oligodendroglioma and astrocytoma of the cerebellum. In ten instances these tumors arose from the cerebellum. In the remaining three cases the tumor presented itself in the fourth ventricle, taking its origin from the medulla in one instance and infiltrating the cerebellum in another. The diagnosis of a primary in contradistinction to a metastatic oligodendroglioma was based on data obtained from autopsy in eight cases, and on presumptive evidence supported by clinical, surgical and laboratory data in five instances.

Metastatic oligodendrogliomas in the posterior fossa have been reported by Greenfield and Robertson[6] (one case), Martin[7] (two cases), Cairns[8] (one case), and Zülch[5] (two cases). These metastases originated from cerebral oligodendrogliomas and spread after years, with or without operative interven-

TABLE 1

Author	*Age and sex*	*Duration of symptoms*	*Signs and symptoms*	*Pathologic findings*	*Definitive surgical treatment*	*Specimen obtained on:*
Van Bogaert and Martin,[15] 1928	Female 27	2 months	Vertigo, retropulsion, nausea, headache, vomiting, papilledema, diplopia, nystagmus, right facial paresis, cerebellar fits	Tumor of cerebellar vermis filling 4th ventricle	None	Autopsy
Van Bogaert and Martin,[15] 1928	Female 24	24 months	Headache, vomiting, secondary optic atrophy, torticollis, right facial paresis and hypacusis, pain in right extremities	Tumor in 4th ventricle	None	Autopsy
Banus and Bueno[16] 1929	Male 15	3 months	Violent headaches, vomiting, head tilted to left, poor vision, ataxia	Tumor in 4th ventricle infiltrating cerebellum	One operation without removal of tumor. Expired 4th p.o. day	Autopsy
Fromment et al[17] 1932	Female 27	5 months	Headache, ataxia, adiadochokinesis, nystagmus, papilledema, paresis of left abducens	Cystic, calcified tumor of right cerebellar hemisphere	None	Autopsy
Agostini,[18] 1933	Male 26	12 months	Headache, vertigo, ataxia, visual disturbances, strabismus, nystagmus, mental disturbances	Cystic tumor, right cerebellar hemisphere, middle peduncle and pons	None	Autopsy
Wertheimer et al,[19] 1935	Male 29	2 months	Headache, vomiting, nystagmus, stupor, papilledema	Cystic tumor, left cerebellar hemisphere	One operation, Good p.o. result	Operation
Garwaki,[20] 1936	Male 13	4 months	Headache, vomiting, ataxia, papilledema	Tumor of left cerebellar hemisphere	None	Autopsy
Garwaki,[20] 1936	Male 18	48 months	Headache, visual disturbances, papilledema	Tumor of both cerebellar hemispheres	None	Autopsy
Juhász,[21] 1942	Male 21	7 months	Headache, nausea, vertigo, papilledema, cerebellar and pontobulbar signs	Diffuse tumor of cerebellum	One operation without removal of tumor. Expired 1st p.o. day	Autopsy
Wycis,[22] 1948	Female 13	1½ months	Headache, dizziness, ataxia—falling to the left, tilt of head to left, cerebellar signs, left, papilledema	Cystic tumor, lt. cerebellar hemisphere	One operation 1945. Pt. well 5½ yrs. later	Operation
Our Case 1	Male 10	2 months	Abdominal pain, headache, nausea, vomiting, drowsiness, nystagmus, papilledema, ataxia	Tumor of cerebellar vermis, calcified with cyst in left cerebellar hemisphere	Three operations (1935, 1943 & 1945) Pt. well Feb. 1951	Operation
Our Case 2	Male 10	18 months	Nausea, vomiting, headache, tilt of head to right, diplopia, papilledema, nystagmus, ataxia	Tumor of 4th ventricle arising from medulla	One operation with poor p.o. result	Operation
Our Case 3	Male 18	7 months	Headache, nausea, vomiting, diplopia, vertigo, ataxia, veering to left, tilt of head to left, papilledema, nystagmus	Mixed cystic oligodendroglioma and astrocytoma, right cerebellar hemisphere	Two operations (1939, 1943) Fair p.o. result	Operation

tion, to the lateral ventricles and third and fourth ventricles. However, the metastases were only encountered in subarachnoid or subependymal location without infiltration of the adjacent neural structures.[5] If this distinction of metastatic from primary oligodendroglioma were borne out by further observations, only the second case of van Bogaert and Martin[15] could be doubted as having been primary in nature, since all the others had infiltrated either the cerebellum or medulla. Furthermore, in two of the three intraventricular tumors in question and in particular in the second case of van Bogaert and Martin, the primary nature of the neoplasm was verified by autopsy.

As far as their pathogenesis is concerned, oligodendrogliomas of the posterior fossa are held to be "essentially midline tumors arising either from the vermis of the cerebellum or other midline structures."[21] In six instances, however, the tumor was described as having occupied one cerebellar hemisphere. In the remaining seven cases the tumor either presented itself in the midline and/or involved one or both cerebellar hemispheres.

The macroscopic appearance is usually that of a well circumscribed tumor of the cerebellum or of the fourth ventricle, soft in consistency and greyish-pink in color. In Juhász's[21] case a diffuse infiltrating tumor of the cerebellum was found on autopsy. This tumor did not present any surface changes and was actually not verified on a preceding suboccipital exploration. Formation of cysts, which is less common in cerebral oligodendrogliomas, was reported in six cases of the 13 subtentorial oligodendrogliomas. This difference contributes, together with the more dangerous location, to the shorter duration of symptoms in the group of posterior fossa tumors. The cysts, usually filled with clear yellow fluid, were only found in the cerebellum.

Microscopically, the oligodendroglioma of the posterior fossa does not appear to differ significantly from that of the cerebrum. The appearance of the characteristic tumor cells is essentially the same. Juhász,[21] however, states that degenerative changes, younger cells and mitoses are rarely seen in the former. Therefore this author feels that the shorter duration of illness in the subtentorial oligodendroglioma group is explained by their more dangerous location rather than by malignancy of the neoplasm. In this connection our case 1 seems to be particularly noteworthy. This patient with a cystic oligodendroglioma of the cerebellar vermis and left hemisphere underwent three operations at 10, 17 and 20 years respectively, and is still alive and according to the last information free of recurrent tumor symptoms more than 15 years after the first operation in June 1935. The comparative studies of the histologic slides of the three different surgical specimens did not reveal any differences in appearance and composition of the tumor. This tumor showed marked calcification. Our case 3 was included in the series although the tumor was a mixed, cystic oligodendroglioma and astrocytoma of one cerebellar hemisphere.

The presence of calcification in one of our cases deserves some comment since Juhász[21] accepts the absence of calcification as rather characteristic for

oligodendroglioma in the posterior fossa, perhaps in analogy to the infrequency of calcification reported in supratentorial midline tumors. Froment, Wertheimer and Dechaume's[17] case showed calcification likewise. In addition, another case of marked calcification in a cerebellar oligodendroglioma, not included in table 1, was observed by Zimmerman.[23] This tumor, according to Zimmerman who also examined the slides of case 1, resembled the latter histologically in every respect. Zülch,[5] who reviewed the midline oligodendrogliomas which involve the thalamus and extend often to the mesencephalon and cerebral peduncles, also reported marked calcification in two out of six cases of definitely substantiated cerebellar midline oligodendrogliomas. It appears, however, that calcification is less frequently present in either group as compared to the oligodendroglioma of the cerebral hemisphere, whereas the spinal oligodendrogliomas showed absence of calcification.[13]

STATISTICS

Among the 13 cases cited there were four females and nine males. The length of illness prior to the first admission to the hospital varied from one and a half months to four years, yet in nine cases the symptoms began within seven months. The average duration of illness prior to admission was ten months and 12 days. Ages of the 13 patients at the time of admission ranged from ten years to 29 years, the average age being 19 years and four months. Due to the limited number of oligodendrogliomas of the posterior fossa, a comparison of their age distribution with that of the more common types of subtentorial gliomas is difficult. According to Cushing as quoted by Bailey,[24] one finds the peak of the medulloblastomas at the age of five to ten years and of the astrocytomas at the age of ten to 15 years. Ependymomas also are more frequent at ten to 15 years although they may occur up to the fifth decade of life. No definite peak is discernable in the age distribution of the subtentorial oligodendrogliomas. However, in seven patients symptoms appeared between the ages of ten to 18 years, and in six patients at an age ranging from 21 to 29 years. There seems to be a definite difference in the age distribution of the subtentorial oligodendrogliomas as compared to those in the cerebrum. The latter show their greatest frequency between 35 and 45 years with a peak at 43 years.[24,5] In this respect the subtentorial oligodendrogliomas seem to have a point in common with the cerebral midline tumors, five out of six occurring below the age of 21 years according to Zülch.[5] This difference does not seem to be entirely explained by the fact that the midline oligodendrogliomas and those of the posterior fossa occupy a strategic position thereby causing appearance of clinical manifestations at an earlier stage in the growth of the tumors.

The clinical symptomatology of the oligodendrogliomas is not particularly different from that of the other gliomas encountered in the posterior fossa. The common symptoms of increased intracranial pressure as well as symptoms of cerebellar and pontobulbar origin were often encountered as can be gathered from the list of the main presenting symptoms in table 1. Impairment

of visual acuity, double vision or other neurologic disturbances of the ocular muscles occur less frequently. Occasionally bulbar symptoms like unilateral hypesthesia or hypacusis have been observed.

Definitive surgical procedures were carried out in seven of the 13 patients. In two instances the tumor was not verified at operation. These patients died on the first and fourth postoperative days respectively. Three of the remaining five patients had a very satisfactory, one a fair and one a poor postoperative result. The surgical case mortality amounted to 28.6 per cent. Since ten posterior fossa explorations including three re-explorations were performed in the seven patients, the operative mortality was 20 per cent.

As far as the relative frequency of subtentorial oligodendrogliomas in relation to other gliomas of the posterior fossa is concerned, no definite figures can be given. However, an estimate of the relative distribution of the oligodendrogliomas as to location in the supratentorial space, posterior fossa and spinal cord can be arrived at. In this connection a recent review of 200 oligodendrogliomas by Ernest, Kernohan and Craig[25] offers additional data. These authors encountered 14 oligodendrogliomas in the posterior fossa, three in the cerebellum, five in the vermis, four in the fourth ventricle and two in the cerebellopontine angle. These cases were not included in the present survey since no detailed reports were offered by the authors. The total number of posterior fossa oligodendrogliomas, including the cases of table 1 and Zimmerman's observation, would thus amount to 28 cases.

A comparison of 409 supratentorial oligodendrogliomas so far reported, in larger series by various groups between 1932 and 1950, with the 28 infratentorial and seven spinal oligodendrogliomas reveals a relative frequency of 92.3 per cent, respectively 6.1 per cent and 1.6 per cent. A correlation of tumor incidence in the different locations to the weight of the normal structures from which the tumors arise, however, shows that the cerebral oligodendrogliomas occur approximately three times as frequent and the spinal oligodendrogliomas twice as frequent per one gram of weight of normal structure as the oligodendrogliomas of the posterior fossa.

SUMMARY

1. A review of the literature disclosed ten case reports of primary oligodendrogliomas arising from structures of the posterior fossa. Three additional cases, including one instance of a mixed oligodendroglioma and astrocytoma, are described. Ten tumors took their origin from the cerebellum. Three neoplasms presented themselves in the fourth ventricle, arising from the medulla in one instance and infiltrating the cerebellum in another.

2. The pathologic characteristics of the tumors as well as the clinical features of the 13 cases, such as duration of illness prior to admission, age distribution, symptomatology and results of operative treatment, are discussed.

3. A total of 28 cases of subtentorial oligodendrogliomas are now on record, including cases which were reported recently although not in detail.

4. An estimate of the relative frequency of oligodendrogliomas in supratentorial, infratentorial space and spinal canal, particularly in correlation to the weight of the normal structures from which the neoplasms arise, is attempted.

The authors wish to express their gratitude to Dr. Abner Wolf for advice and help.

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Headache in Ophthalmic Practice

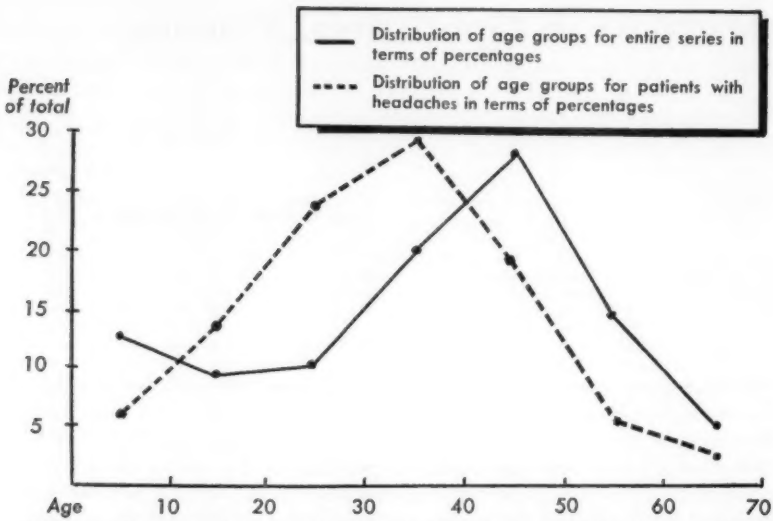
Abraham J. Lanchner, M.D.

THE ophthalmologist is often consulted to ascertain the cause of headache in patients who complain of this symptom. Headache is the result of so many different disorders that it was thought worth while to make this study of over 3,000 cases to determine the relative importance of the eye in the etiology of headache. Numerous papers have been written on this subject, but few give statistical data.[1] Most of the papers are speculative, giving only the authors' impressions. Notable exceptions are those of Snell[2] and Post,[3] whose conclusions are based on an analysis of a group of patients. Ruedemann[4] determined the incidence of headache as a chief complaint in a series of 200 general medical cases, but gave no further figures.

Wolff[5] emphasized the importance of headache when he stated that, "The examination for military service in World War II of 10,000 unselected men between the age of 18 and 38 revealed that headache is the most common bodily complaint. About 8 per cent of these citizens had frequent severe headaches. Fifty per cent of men who after induction demonstrated by trial their temperamental unfitness for war complained of headache."

The present study was undertaken to determine first, what the incidence of headache is in ophthalmic practice, and second, to determine if possible the cause of these headaches. A series of 3216 consecutive patients who wished to have their eyes examined because of ocular symptoms, headaches, or other complaints, is reviewed. Many of these patients were referred by other physicians, usually because of the symptom of headache. This series represents the average range of ophthalmic practice and is not weighted in any way. If the patient did not voluntarily complain of headache, he was questioned about it. He was always asked about the location of the headaches, when they first appeared, their frequency, time of onset, duration, association with the use of the eyes, whether they were relieved by sleep, whether present on arising, and what associated symptoms were present. Pain in the eyes or face was not considered to be headache. Since children are sugges-

From the ophthalmological service of Montefiore Hospital, New York City.



tible, considerable care was necessary in obtaining a reliable history. All the patients were given a complete ocular examination. Those patients whose headaches were apparently due to refractive errors were given refractive correction. Orthoptic exercises were given when indicated.

The following figures give the total number of patients examined, the number of those who complained of headache, and the sex distribution.

Total number of cases	3216	
Males	1640	51 per cent
Females	1576	49 per cent
Cases with headache	355	11 per cent of total
Males	148	41.7 per cent
Females	207	58.3 per cent

Of the 3,216 patients examined, the division between the sexes was almost equal, 49 per cent females and 51 per cent males. Three hundred and fifty-five, or 11 per cent of the entire group, complained of headache. This is in close agreement with the pre-induction World War II finding of 8.5 per cent. Ruedemann[4] found headache to be the presenting symptom in 25 per cent of 200 medical records which he reviewed, and Post,[3] in his series of 610 cases which came for ophthalmic examination, found an incidence of 30 per cent.

The sex distribution of the patients complaining of headache shows 148 males and 207 females, or 16.6 per cent more females than males. This finding also is in agreement with that of other writers. Snell[2] in his series of patients who came for ophthalmic examination, found that out of 318 cases of headache, 84 per cent occurred in females.

The age distribution by decades is shown in the form of a graph in figure 1. Most of the patients were in the fourth, fifth and sixth decades, with the

TABLE 1

PATIENTS WITH HEADACHE — POSITIVE OCULAR FINDINGS — REFRACTIVE

Diagnosis	M	F	T	*Males*	*Females*	*Total*	*Pct. of Total*
Astigmatism				34	54	88	61
Myopic	16	14	30				
Comp. myopic	6	9	15				
Hyperopic	6	20	26				
Comp. hyperopic	6	10	16				
Mixed		1	1				
Presbyopia				12	16	28	19
Hypermetropia				3	11	14	9
Overcorrection				2	5	7	5
Myopia	2	1	3				
Miscellaneous	0	4	4				
Emmetropia (needless correction)				1	2	3	
Induced prism (glasses off center)				0	2	2	
Anisometropia				1	0	1	
Myopia (high)				0	1	1	
Amblyopia (correction caused headache)				0	1	1	
Total				53	92	145	

greatest number in the fifth decade. The greatest number of patients with headaches were in the third, fourth and fifth decades, with those in the fourth decade comprising the largest group.

ETIOLOGY

There were 184 patients in whom there was objective evidence of ocular disorders (tables 1 and 2). This represents 52 per cent of those with headache. Table 1 is restricted to errors in refraction. Here it is noticed that of the total of 145 patients, 88 or 61 per cent had astigmatism of one form or another. This is in very close agreement with Snell's[2] finding of 64 per cent. Next in the order of frequency came presbyopia, 19 per cent; hypermetropia, 9 per cent, and overcorrection, 5 per cent. The other findings in this table are represented by too few cases to be of any statistical value, but are interesting nevertheless. There were three emmetropes who wore an unnecessary correction, two patients whose glasses were off center, and one each of anisometropia, high myopia and amblyopia in whom the correction of the amblyopic eye caused headache.

TABLE 2

PATIENTS WITH HEADACHE — POSITIVE OCULAR FINDINGS — MUSCULAR IMBALANCE

Diagnosis	*Males*	*Females*	*Total*	*Pct. of Total*
*Convergence insufficiency	13	14	27	65
*Accommodation weakness	4	8	12	30
Divergence excess	0	1	1	
Exotropia—inconstant	1	0	1	
Total	18	23	41	

*There were two cases of combined convergence insufficiency and accommodation weakness. They were both females in fourth decade of life.

TABLE 3

PATIENTS WITH HEADACHE — NON-OCULAR FINDINGS

Diagnosis	*Males*	*Females*	*Total*	*Pct. of Total*
Cause undetermined	27	37	64	37
Emotional tension	25	32	57	33
Migraine syndrome	10	6	16	9
Sinusitis	7	9	16	9
Vascular	3	4	7	4
Hypertensive 5				
Arteriosclerotic 2				
Central nervous system	3	2	5	3
Pituitary tumor 1				
Temporal lobe tumor 1				
Cerebral aneurism 1				
Rotary nystagmus 1				
Concussion 1				
Neuralgia	2	2	4	3
Head cold	0	1	1	
Post grippe	0	1	1	
Total	77	94	171	

There were 39 patients with muscular imbalance (table 2) who complained of headache. The corrected figure is 39 instead of 41 because two patients had both convergence insufficiency and accommodation weakness and were therefore counted twice. Twenty-seven, or 65 per cent, had convergence insufficiency, and 12, or 30 per cent, had weakness of accommodation. There was one case each of divergence excess and exotropia of the inconstant type. The numbers are too small to draw conclusions concerning the sex and age distribution.

The group complaining of headache without associated ocular findings (table 3) consisted of 171 patients, approximately 48 per cent of the entire headache group. Here also the females predominated, but only by 10 per cent. In 64, or 37 per cent, the cause of the headache could not be determined. Emotional tension came next with 57, or 33 per cent, followed by migraine syndrome and sinusitis, each with 16 patients, or 9 per cent. Patients in the other subdivisions in this table were few in number, but of great importance nevertheless, especially those suffering from disease of the central nervous system.

It should be noted that out of a total of 355 patients complaining of headache, 184, or approximately 52 per cent, had positive ocular findings. In other words, over 50 per cent of all patients in this series who complained of headache, had associated ocular findings.

CORRELATION BETWEEN LOCUS AND CAUSE OF HEADACHE

An attempt was made to correlate the location of the headache with etiology (table 4). In the group with positive ocular findings, 86 per cent of the headaches were frontal. Next in order of frequency came occipital (7 per cent), temporal (6 per cent) and vertex (1 per cent). Weeks[6] stated that

TABLE 4

CORRELATION OF DIAGNOSIS AND LOCUS OF HEADACHE

Ocular Diagnosis	*Frontal*	*Occipital*	*Temporal*	*Vertex*	*Entire Head*	*Sub-occipital*
Astigmatism	77	5	8	1		
Presbyopia	25	1	2	1		
Hypermetropia	14					
Total (Astig., Pres., Hyp.)	116	6	10	2		
Convergence insufficiency	25	5				
Accommodation weakness	12	1				
Total (muscular imbalance)	37	6				
Total (all ocular)	153 (86%)	12 (7%)	10 (6%)	2 (1%)		
Non-Ocular Diagnosis						
Cause undetermined	43	11	10	7	3	
Nervous tension	27	19	6	2	7	2
Migraine syndrome	12	1	4		1	
Sinusitis	15	2		1	1	
Vascular	3	4	1	1		
Central nervous system	4				1	
Head cold					1	
Post grippe		1				
Neuralgia		1	1	2	1	
Totals	104 (53%)	39 (20%)	22 (11%)	13 (7%)	15 (8%)	2 (1%)

75 per cent of ocular headaches were frontal, and Post[3] found 66 per cent to be frontal, with occipital headaches next in frequency.

In the non-ocular group there is a striking difference in the locus of the headache. Only 53 per cent were frontal, followed by 20 per cent occipital, 11 per cent temporal, 8 per cent entire head, 7 per cent vertex and 1 per cent suboccipital.

DISCUSSION AND SUMMARY

These cases of headache occurred in a consecutive series of patients who consulted an ophthalmologist. The incidence of headache and the type of head pain encountered is undoubtedly different from that found in other types of practice. Many patients with headache are eliminated before they reach the ophthalmologist. In this series 11 per cent of the total complained of headache.

The symptom of headache was most frequently encountered in the early adult and middle age years.

Of all the patients who complained of headache, approximately one-half, or 52 per cent, had associated ocular findings. This preponderance of ocular findings would undoubtedly not exist in a series based on a different type of practice. Astigmatism in 88 cases, or 61 per cent, was the chief ocular finding, followed by presbyopia in 28 cases, or 19 per cent, and surprisingly only 14 cases, or 9 per cent, of hypermetropia, and only one case of high myopia. It should be emphasized that not every patient with a refractive error or muscle imbalance suffers from headache; only a small percentage do so. Only 184,

or 5.7 per cent, of all the patients in this series of 3,216 cases who complained of headache had positive ocular findings, whereas the great majority of patients who were examined had an error of refraction, muscle imbalance or other pathology. Wolff[5] offers a plausible explanation why some patients suffer from headache and others with the same defect do not. He believes that in addition to an error of refraction or muscle imbalance there is a state of emotional tension, so that there is a cumulative effect of two factors, either one of which in itself could cause headache. Monch[7] makes the interesting observation that headache is a common complaint in psychoneurotic patients, but is rare in psychotic patients.

It has been demonstrated that in all the groups more females than males had headaches. In the group with refractive errors there were 26 per cent more females than males, in the group with muscle imbalance 12 per cent more females, and in the group without associated ocular findings 10 per cent more females. It may be concluded from this that females are more sensitive to noxious stimuli than males, and that they are more subject to states of emotional tension.

In all the groups frontal headache predominated, but the incidence of this type of headache was greatest in the group with associated ocular findings, 86 per cent compared with 53 per cent in the group without associated ocular findings.

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The indications of brain disease that are revealed by the ophthalmoscope are not only of the highest practical importance, but are of interest as a salient indication of the progress of medical science, since thirty years ago they were unknown. Morbid appearances in the eye are frequent in intracranial disease, and often prove the existence of such disease when other symptoms are inconclusive, or afford evidence of its nature that can be obtained from no other source. For this and other reasons, skill in the use of the ophthalmoscope, and familiarity with the conditions it reveals, are indispensable to the physician.

—Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Treatment of Headache with Ergotamine-Caffeine Suppositories

Kenneth R. Magee, M.D., Martha R. Westerberg, M.D. and Russell M. DeJong, M.D.

ERGOTAMINE TARTRATE, first introduced for the symptomatic treatment of migraine by Maier[1] in 1926, has been found to be the most specific drug for relief of this type of headache. Statistics on its efficacy vary with different observers, but it is generally conceded that if administered early enough in the attack, ergotamine tartrate either aborts or completely relieves migraine and certain related vascular headaches in from 70 to 90 per cent of cases.[2] In fact, it is so specific that it may be used as a therapeutic test for migraine. Studies by Wolff[3] and others have demonstrated that the pain in migraine is produced by dilatation of certain cranial arteries, and the therapeutic effectiveness of the drug is due to the vasoconstriction which it produces. Ergotamine tartrate is much more effective if given parenterally (subcutaneously, intramuscularly, or occasionally intravenously) than if administered by mouth, but parenteral administration is definitely less practical for the majority of patients, especially because the drug must be given at the very onset of symptoms. Another drawback to parenteral administration is the frequency with which it causes gastrointestinal disturbances. Oral ergotamine tartrate is less effective because of its delayed absorption. Gastric motility is greatly reduced with the onset of headaches in most patients. Oral ergotamine tartrate is enteric coated, and this, together with reduced gastric motility, results in such slow absorption that the headache has advanced in severity before any effect of the drug is experienced, and by that time may be irreversible.

Recently it has been found that a new compound, Cafergot, which is a combination of 1 mg. of ergotamine tartrate, together with 100 mg. of caffeine, is more effective in many patients than ergotamine alone;[4] there are fewer side effects, and the amount of ergotamine needed to control the headache may be reduced. Possibly the added caffeine works synergistically with the ergotamine. Friedman[5] suggests that the caffeine acts by causing further cerebral vasoconstriction, bringing about psychic stimulation, and perhaps by increasing the rapidity of the absorption of the ergotamine. Cafergot thus far has been available only in a sugar-coated tablet for oral administration, and if large doses of ergotamine are needed, it is necessary to administer a rather

From the department of neurology, University Hospital, University of Michigan, Ann Arbor, Michigan.

large dose of caffeine if the headaches are treated with Cafergot alone.

This paper reports experience with ergotamine tartrate and caffeine administered by rectum. The potential advantage of this route is prompt absorption, approaching that obtained by hypodermic injection. Therefore, patients in whom oral ergotamine compounds fail to give adequate relief, or in whom vomiting precludes the use of oral medication, may be able to receive benefit from rectal administration. Preliminary reports on the use of ergotamine-caffeine suppositories in the treatment of migraine have been made.[6,7,8,9,10]

PROCEDURE AND RESULTS

A total of 100 patients treated on the neurology service of the University Hospital were given suppositories of either 2 mg. of ergotamine tartrate and 100 mg. of caffeine (E.C. 112), 2 mg. of ergotamine tartrate and 200 mg. of caffeine (E.C. 222), or 2 mg. of ergotamine tartrate, 100 mg. of caffeine and 0.25 mg. of Bellafoline substance (E.C.B. 115)*

One group of patients with typical migraine, another with the so-called histamine headaches of Horton,[11] and a third group classified as having tension or psychogenic headaches were studied. Each patient was advised to take one suppository at the onset of his next headache. Where the suppository gave no relief, yet produced no side-effects, two suppositories were prescribed for the next headache. If one suppository gave relief but caused unpleasant side effects, a dosage of one-half or occasionally one-fourth suppository was advised to ascertain that dosage giving maximal relief without serious side effects.

TABLE 1

		Results					
		Excellent		Good		Poor	
Type of Headache	*Number*	*Number*	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Migraine	57	35	62	12	21	10	17
Histamine headache	20	4	20	10	50	6	30
Tension or psychogenic	23	0	0	3	13	20	87
Totals	100	39	39	25	25	36	36

The results are presented in table 1, and are classified as excellent, good or poor. In the migraine and tension groups the classification "excellent" was used if the patient experienced complete relief from headache within two hours. Classification as "good" meant that there was substantial but not complete relief within four hours. Results were described as "poor" in patients who found little or no benefit or in whom side effects precluded the use of the drug. As the usual histamine headache is much shorter in duration than the above types, the medication had to completely relieve the pain within one-third of the average length of time of the patient's headaches to have the results classified as "excellent," or had to give significant relief above that ob-

*These compounds were furnished by the Sandoz Pharmaceuticals Division of Sandoz Chemical Works, Inc., New York 14, New York.

tained by other medication within one-half of the average duration of the patient's headaches to be classified as "good."

Side effects of the medication consisted of nausea, vomiting, cramps in the abdomen and legs, lightheadedness, numbness of the extremities, palpitation, sweating and sleepiness. The only frequent and significant complaint was nausea, which appeared in 25 patients. By properly regulating the dosage it was rarely found necessary to discontinue the medication because of untoward reactions. Women had a higher incidence of side effects than men, and therefore their dosage was often decreased. This was very important, inasmuch as several patients would have been forced to discontinue the medication, even though it gave good relief of headache, were it not for the reduction in dosage. As the study progressed it became routine to advise one-half of a suppository as the initial dose, and it was found that more than one suppository rarely increased the drug's effectiveness.

Twenty-one patients with migraine had previously received oral ergotamine compounds, and all of these stated that the suppository was superior in that it either gave more prompt and efficient relief, or produced fewer side effects. Only three comparisons between the oral and suppository use of ergot were possible in the group of patients with histamine headaches. Two of these preferred the suppository; one found the suppository definitely less effective than the oral compound. Seventeen patients with migraine were able to compare the suppositories with hypodermic injections of ergotamine tartrate (Gynergen) or with D.H.E. 45. Of these, three preferred the suppository to injection, ten patients noted no significant difference, and four thought that the injection was definitely superior to the suppository. Only two patients in the group with histamine headaches could make similar comparisons, one preferring the injection to the suppository, the other patient noting no difference.

The majority of patients using the suppositories for migraine stated that it was the most effective medication they had ever taken for their headaches. Comparing the three types of suppositories, no appreciable difference was found between them. The effectiveness and side effects depended primarily on the total dosage of ergotamine and not on the relative amount of caffeine present or the addition of the Bellafoline. As is true with other routes of administration, it was observed that maximum effectiveness is obtained only when the suppository is used at the very onset of the headache.

DISCUSSION

The present results parallel those of Fuchs and Blumenthal,[6] who obtained 85 per cent excellent results in the treatment of migraine, using different criteria for classification, but disappointing results in tension headache (poor response in nine of 13). Cohen and Criep[7] reported good results but found that 11 of 25 patients preferred oral Cafergot to the suppositories, eight preferred the suppositories (E.C. 112) and six patients noted no difference. Kadish[8] likewise found good results with the use of E.C. 112 but in addition reported five of a series of ten patients with psychogenic headache obtaining

excellent results with E.C. 112. Friedman and von Storch[9] reported 76 per cent success with the use of E.C.B. 115 suppositories, but found that only 27 per cent of patients improved with rectal E.C. 222. In their series, however, oral Cafergot gave the best results, with 86 per cent improvement. Ryan[10] stated that in his experience the suppositories gave no better results than the oral preparation, and in most cases they were not as good. Final conclusions will have to await the compilation of larger statistics but it appears that rectal administration of ergotamine and caffeine may occupy a useful position in the treatment of migraine and related headaches.

SUMMARY

A series of 100 patients with migraine, histamine and tension headaches received a therapeutic trial of suppositories containing ergotamine tartrate and caffeine. Three preparations were tested.

The use of suppositories was successful in a large percentage of patients with migraine and in a smaller percentage of patients with histamine headaches, but was disappointing in patients with tension or psychogenic headaches.

Side effects were typical of those produced by ergotamine in any method of administration and were usually easily eliminated by proper adjustment of dosage. The optimal dosage was from one-half to one suppository.

The rectal administration of ergotamine and caffeine promises to offer relief to many patients with migraine or related vascular headaches in whom oral ergotamine compounds either give no relief or cause serious side effects.

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A Comparison of Provocative Agents in the Epilepsies and in Controls

Robert Cohn, M.D., John E. Nardini, M.D.
and Wade H. Boswell, M.D.

In an attempt to attain a higher correlation between clinical seizures and the electric abnormalities that are ordinarily accomplished in the "spontaneous" interseizure electroencephalographic tracings, various provocative agents have been employed.[1–5]. Aside from hyperventilation, which in this communication is considered as part of the "spontaneous" activity, sleep, insulin-induced hypoglycemia and intravenous Metrazol were utilized. In this study, more than 1000 sleep records, somewhat more than 200 insulin-induced hypoglycemia reactions, and 183 recordings on individuals subjected to intravenous Metrazol have been obtained. These provocative procedures definitely raised the percentage of positive correlations. Because of these results, an attempt is made to evaluate precisely the relative effectiveness of the three procedures in a group of individuals in whom each of the above provocative agents was administered successively. A total of 41 patients were studied, 26 of whom were known to have clinical epileptic discharges. Fifteen of the subjects were "controls" in the sense that no convulsive phenomena were observed or recorded at any time during the life history. The patients ranged between the ages of 17 and 43 years of age.

METHODS

Sleep was ordinarily of the natural type, but in certain cases Seconal, sodium Amytal and sodium Pentothal were used to induce sleep. Aside from the early drug effect (fast activity), the sleep attained did not appear appreciably different from that seen under normal conditions. Only the "early" phases of sleep are considered in this report; that is the output occurring during the production of "spontaneous" and induced K-complexes and biparietal spikes, during runs of approximately 14 per second activity, and during the high voltage slow wave phases.

Insulin-induced hypoglycemia was accomplished by administering to the fasting patient 0.1 unit (40 units per ml.) per kilogram of body weight of

From the United States Naval Hospital, Bethesda, Maryland.

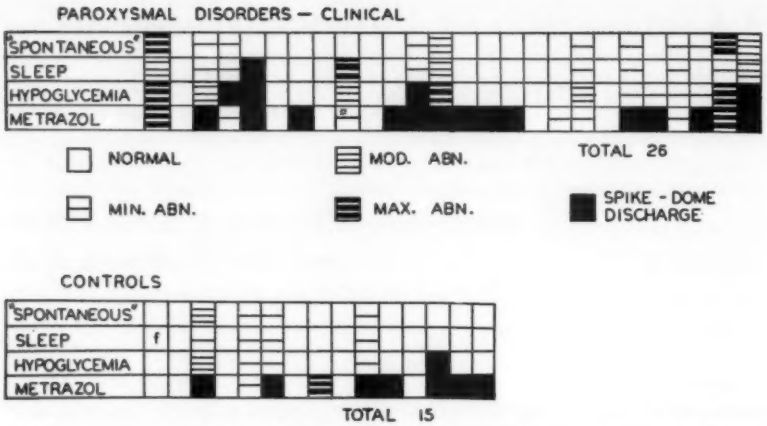

FIG. 1.—Composite results. * Indicates that clinical automatism was induced. f Signifies the presence of a dominant amount of fast activity during natural sleep.

insulin. The fasting blood sugar, and the value of the blood sugar at the termination of the test were determined by the Benedict-Folin method. The electrocardiogram was always simultaneously recorded with the electroencephalogram in these cases because a small number of patients in relative hypoglycemia produce ventricular extrasystoles and other disconcerting heart dysrhythmias that sometimes necessitate termination of the test.

Metrazol was diluted so that 300 milligrams was contained in 9 ml. of sterile water. This was injected intravenously, at the rate of 100 milligrams (or 3 ml.) per minute. At the production of the first spike-dome discharge, or with the elicitation of persistent focal slow wave activity, the administration was stopped and followed immediately by 300 to 500 milligrams of sodium Amytal intravenously (using the same needle, but interchanging syringes). In this way an attempt was made to limit the number of grand mal convulsions during the test. The limitation of major seizures was particularly important in the development of a large control series, in that the morale and cooperation of the subjects dropped precipitously when a series of major convulsive episodes occurred.

RESULTS

Of the 26 patients with indisputable evidence of convulsive disorder, none showed spike-dome activity in the "spontaneous" tracings. Sleep gave rise to or accentuated the "spontaneous" electric abnormality in only two cases, producing spike-dome activity in one instance. Under insulin-induced hypoglycemia significant electric changes occurred in seven cases, four with spike-dome activity. Metrazol activation produced marked electric abnormality in 14 individuals, 13 of whom generated spike-dome discharges. It must be

emphasized that the production of a minimal to moderate amount of slow activity, particularly that which was symmetric in the homologous frontal and temporal derivations was never considered as evidence of important changes in the electroencephalogram in this series of cases. This restraint was particularly important in the hypoglycemia states. In the 15 selected control cases in which there was no clinical evidence of any type of a convulsive disorder, seven patients generated spike-dome activity when subjected to intravenous Metrazol. Only one individual showed spike-dome activity under insulin-induced hypoglycemia. Sleep was productive of no variation from the basic "spontaneous" type of electroencephalogram. A tabulation of the results is shown in detail in figure 1.

CASE REPORTS

Case 1 is representative of the findings in certain individuals subject to convulsive disorders. The patient was admitted to the hospital on April 26, 1950 because of an interval of unconsciousness. It was stated he exhibited tonic and clonic movements of all extremities and that there was a state of "confusion" which existed for approximately one hour following the gross seizure.

In January 1949 the patient had first noted involuntary jerking movements of the upper extremities. These attacks occurred three to four times per week thereafter. Until the episode which necessitated hospitalization the patient insisted that he had never lost consciousness. He stated that he had previously been hospitalized to determine the cause of the involuntary motor discharges. He stated further that, following a careful study at a civilian hospital, including a pneumoencephalogram, he was told that he had a "minor form of epilepsy." The family history showed that both parents were living and well and that nine siblings were living; one brother was said to require repeated hospitalization because of a chronic chest condition.

Careful clinical studies at the U. S. Naval Hospital, Bethesda, Maryland, showed no significant variations from normal. Glucose tolerance tests were within normal limits. Blood and spinal fluid serology were negative. Following admission to this hospital the patient had several seizures; ordinarily they occurred upon arising in the morning. At these times his arms abducted suddenly in myoclonic activity, frequently followed by generalized tonic and clonic discharges and unconsciousness. Occasionally during the witnessed attacks he bit his tongue; he was usually cyanotic and always bewildered after each major seizure. The "spontaneous" electroencephalograms were repeatedly within normal limits, but all types of activation procedures showed short sequences of 3 per second spike-dome activity. This is shown in figure 2. On Tridione therapy the patient showed a diminution in intensity and frequency of seizures.

Case 2 is representative of a non-convulsive, selected control subject. This 18 year old man was admitted to the sick list because of a self-inflicted laceration transversely across the palmar surface of the left wrist. He stated that prior to this act he had noted a progressive blurring of vision which induced great anxiety because of the probable curtailment of his service career.

The patient stated that he was said to have "been born dead, and didn't come to life for about 15 minutes." He had chickenpox at five years, scarlet fever at six years, measles at nine years of age. He stated that he was rendered unconscious for approximately 15 seconds by a blow on the head with a beer bottle a "few years ago." He could not elaborate the statement; there was complete denial of any other intervals of unconsciousness. The patient was a good student in grammar and private schools. He stated he never was truant from school. His favorite subjects were English literature and mathematics. On describing himself the patient stated that he was "lazy, easy to get along with." He stated that he liked fun and enjoyed being studious.

During hospitalization the patient was neatly attired. His behavior was described as "superficially silly without regard to the seriousness of his immediate difficulty." Content

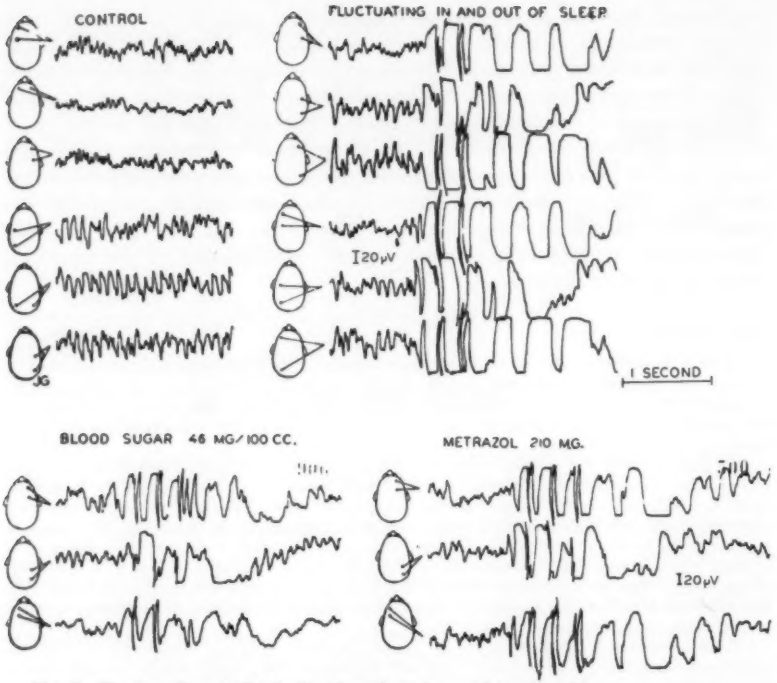

FIG. 2.—Tracings from individual with a clinical convulsive disorder.

of thought revealed no bizarre material. Mental grasp and capacity appeared above average. The language function was adequate in mechanics and ideation.

Insulin-induced hypoglycemia on November 11, 1950, gave rise to bursts of high voltage slow activity with occasional isolated spike-dome discharges. The blood sugar at the time of this electric output was estimated at 43 mg. per 100 ml. of blood. The fasting glucose level was measured at 93 mg. per 100 ml. of blood.

On November 13, 1950, 230 mg. of Metrazol generated high voltage spike-dome discharges. Following the administration of sodium Amytal the patient slept. On being awakened he stated that he felt "groggy"; the speech output was slurred but adequate. Except for moderate nystagmus, nothing remarkable was observed. Upon ambulatory return to the ward he was said to have had an "hysterical like" episode, during which he sobbed. This was followed by sleep. Samples of the recordings obtained with the various provocative tests are seen in figure 3.

DISCUSSION

In this series of patients "sleep" as a provocative agent, using the criterion of spike-dome activity as the determinant of abnormality, generated negligible positive results. In a much larger series of cases, in which only one other mode of activation besides sleep was employed, similar relatively negative results have also been obtained. However, in this latter unselected series, to be reported later, occasionally foci of electric abnormality were elicited that were

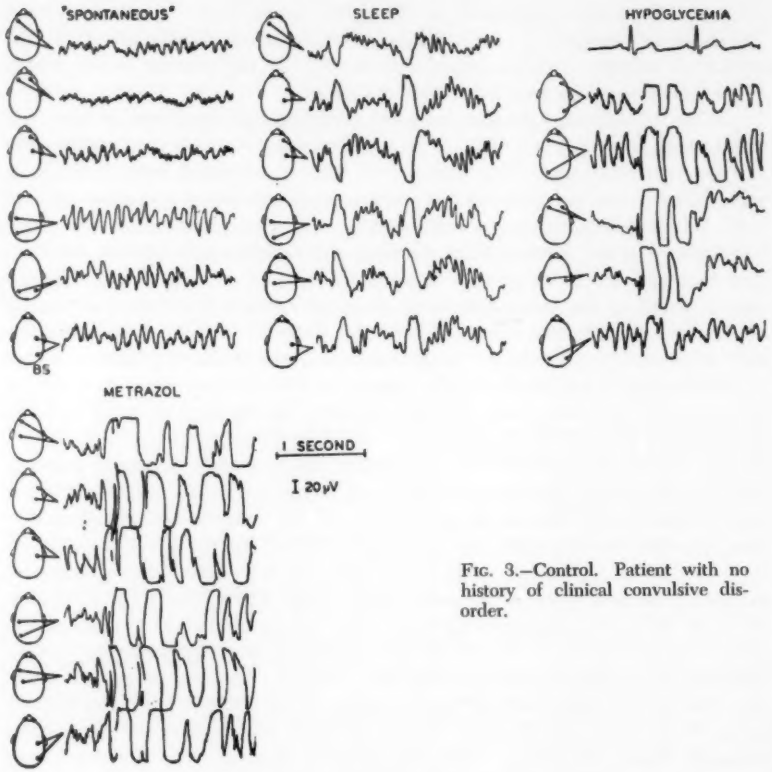

FIG. 3.—Control. Patient with no history of clinical convulsive disorder.

not present in the "spontaneous" record. Of further interest in this larger "sleep" series, several patients, particularly those with old vascular lesions, who showed focal slow activity in the "awake" record, gave rise to generalized slow activity during "sleep."

The elicitation of spike-dome activity during insulin-induced hypoglycemia in four out of 26 epileptic patients appears high when compared with the results in a large series of cases (over 200) where this was the sole provocative agent. In the latter group (all epileptics) it was observed that the per cent of positive correlations was increased only somewhat over 6 per cent in patients whose "spontaneous" electric records showed no abnormal characteristics.

Using Metrazol as the activation agent half of the epileptic patients (or one in every two) showed spike-dome discharges. In a larger series of 75 patients with known seizures, in which sleep and insulin-induced hypoglycemia were not performed, Metrazol generated spike-dome discharges in 31

subjects. Forty-two individuals in the latter series showed entirely normal "spontaneous" recordings. This larger series therefore closely attests to the statistical stability (within reasonable limits) of the smaller series which forms the primary part of this communication.

Of the 15 controls who gave no history in personal interviews or were not observed to have any intervals of unconsciousness, seven showed spike-dome activity with Metrazol. This group was heavily weighted with individuals with disorders of sleep (narcolepsy) and patients exhibiting aggressive clinical behavior. In a larger series of control patients in which an attempt was made to take "unselected" patients from the neuropsychiatric wards,[6] it was observed that in a total of 118 subjects 17 showed spike-dome activity; a frequency of one in seven. If the individuals with sleep disorders and the most obviously aggressive subjects were removed from the statistics in this latter series, the ratio of positive (spike-dome) responses falls closer to one in ten.

Of theoretical significance is the amount of Metrazol necessary to detonate discharges in the control and epileptic patients. In the total series of patients it was found that no clearcut threshold could be established. Certain control patients had discharges with less than 100 mg. of Metrazol. However, patients who spontaneously generated spike-dome activity during hyperventilation often required only around 100 to 180 mg. of the drug to elicit the first discharge (often accompanied by myoclonic action). In the great majority of the controls, as well as in subjects with clinical convulsive phenomena, 230 to 290 mg. of Metrazol was the usual firing range. Occasionally the discharge occurred after the cessation of Metrazol and during the first 10 seconds of the sodium Amytal injection. It is of interest also that in our experience the administration of intravenous Tridione did not influence the slow output (if present); this was in direct contrast to the sodium Amytal where the characteristic fast activity obliterated the slow waves within 20 seconds after the start of the administration of the drug. (One ml. of the sodium Amytal (100 mg.) was administered as rapidly as possible; the remainder, up to 500 mg. in certain cases, was injected slowly.)

The observation of definite, indisputable spike-dome activity in patients who have normal spontaneous electroencephalographic patterns, and who have had no history of any type of convulsive phenomena, forces one to recognize that even the spike-dome discharge is not diagnostic of or synonymous with the clinical syndrome of petit mal epilepsy. Even more, the results in the control series forces one to the viewpoint that the spike-dome activity discharge is not precisely correlatable with clinical epileptic phenomena, even in a very general concept. However, the results in the control subjects might indicate that certain patients, now diagnosed as psychotic (on a behavioral level), may owe this asocial behavior primarily to disturbed neuronal discharges and that the observed mal-behavior is the result of the demands of and his response to society. Or more simply, the aggressiveness and other asocial behavior may be primary and not the overt expression of hostility to authoritarian figures.

CONCLUSIONS

1. Sleep was the least important provocative agent used in this series of cases.

2. The electric changes induced by insulin hypoglycemia correlate well, but insufficiently frequent, with clinical epileptic disorders.

3. Metrazol is the most potent generator of spike-dome activity among the provocative agents used.

4. Spike-dome activity as elicited by provocative agents is not pathognomonic of, or completely correlatable with, clinical epileptic discharges.

5. Intravenous Metrazol appears to be an exceedingly important procedure to employ in all cases where clinical epilepsy is suspected and not confirmed by the usual electrical studies. However, it should be emphasized that in the use of Metrazol, clinical judgment must still be decisive in the final interpretation of results.

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No disease can illustrate the pathology of the excito-motory system better than epilepsy. It is sometimes centric, and incurable; frequently eccentric, arising from gastric or intestinal irritations, and curable. It involves every part, and every function of which I have spoken under the head of the physiology. The fourth and sixth nerves are affected, and the eyes move convulsively; the tongue is protruded, the teeth are forcibly closed upon it, the mouth is variously moved, with the extrusion of bloody foam; the larynx is closed, and there are forcible convulsive efforts of the expiratory muscles; and, as I just stated, the sphincters are sometimes relaxed, and the ejaculators occasionally expel the semen.

—Marshall Hall in *Lectures on the Nervous System and its Diseases*, published in 1876.

Subacute Encephalitis

Three Year Survival With Long-Term Remission

William M. Landau, M.D. and Joseph J. Gitt, M.D.

Dawson[1] first described an encephalitis characterized pathologically by cellular inclusion bodies and clinically by a subacute to chronic progressive course. Other cases were reported by Akelaitis and Zeldis,[2] Brain, Greenfield and Russell,[3] Greenfield,[4] and Malamud, Haymaker and Pinkerton.[5] Their clinical and pathologic similarity to the subacute sclerosing leukoencephalitis of van Bogaert[6] was pointed out by Malamud, Haymaker and Pinkerton and by Greenfield. The fact that inclusion bodies have only occurred in islands of gray matter in some reported cases makes their apparent absence in others indeterminate. Inclusion bodies have also been found in cases of herpes simplex encephalitis from which that virus was isolated.[7,8] It is not clear whether the inclusions in these acute cases differ pathologically from the subacute encephalitis group.

Whether or not subacute inclusion encephalitis is related pathologically to subacute encephalitis without inclusion bodies,[6,9] the two types cannot be distinguished clinically. The characteristic picture, with some exceptions, consists of insidious onset of mental symptoms in the first or second decade. As the condition progresses patterned jerky spontaneous movements appear as well as other types of seizures. Mental deterioration is rapid and a variety of neurologic defects may develop. The course is usually afebrile, except terminally, and cerebrospinal fluid examination is usually negative. Death occurs within one year and often after a few months. A few cases of longer duration have been described. A viral etiology has been presumed but thus far no virus has been isolated.

In spite of the occurrence of spontaneous remissions in a few of the reported cases, none has presented the marked remission of long duration which characterizes the case to be reported. Beginning improvement coincided with a course of antibiotic therapy.

From the department of neuropsychiatry, Washington University School of Medicine and St. Louis City Hospital, St. Louis

Work supported in part by fellowship grant from the National Paraplegia Foundation.

REPORT OF A CASE

A 10 year old boy was admitted to St. Louis Children's Hospital in March 1948. For the preceding three months he had nocturnal fainting spells which increased in frequency until they recurred almost nightly. During these he became pale, lost consciousness, and fell limply. Temper tantrums and other evidences of personality change had been noted for several weeks prior to admission.

Birth and development were essentially normal and there was no family history of neurologic disease. Infectious disease history was irrelevant except for a mild pertussis infection in September 1947; at about that time he complained of right-sided headache over a two week period. In the following months he did poorly in school, whereas previously he had done well.

Physical and neurologic examinations were negative at admission except for indistinct optic disc margins and diplopia for near objects. Visual fields showed slight enlargement of blind spots. Routine urine and blood examinations (including serologic test for syphilis) were negative. The white blood cell count was 7,500. Spinal fluid pressure was 170 mm. and 6 polymorphonuclear cells per cu. mm. were reported. Total protein was 54 mg. per cent. Two electroencephalograms revealed a slow paroxysmal dysrhythmia with a left occipital focal trend (figure 1A). Skull x-rays and pneumoencephalogram were normal. The hospital course was uneventful and the rectal temperature varied between 36.2° and 37.6° C. The patient was discharged in April 1948 on anticonvulsant medication.

By July 1948 the fainting spells had decreased in frequency and he angered less easily. However, he had lost 3 pounds in weight, and acted strangely. The left optic disc margins remained blurred. Rapid succession movements of the hands were poorly performed and the finger-nose test was done somewhat inaccurately, more so on the left. Later he was observed to stumble often, incoordination increased, and his speech became incoherent. The electroencephalogram became more disordered than previously and there were high amplitude slow waves in the occipital leads (figure 1B).

In August 1948 he showed frequent transient lapses accompanied by sudden drooping of the head, and was chronically hungry, quarrelsome and irritable. He also had several falling spells which occurred daily in spite of anticonvulsant medication. A psychometric survey in October 1948 showed no definite organic deficit, and the child was described by the psychologist as emotionally immature and retarded.

In November 1948 he fell backwards in his spells with arms extended and fingers stiffened. Thereafter he was unconscious for 20 to 40 minutes. He was hospitalized again and all medication was withdrawn; then jerking seizures of the head and arms commenced and recurred at intervals of a few minutes. Combined electroencephalogram and electromyogram recording showed no temporal correlation between brain and muscle activity. A later electroencephalogram was still moderately disordered but improved (figure 1C). The basal metabolic rate was −16. Routine laboratory studies were negative. Oral temperatures ranged betwen 36.0° and 37.4° C. On January 6, 1949 the patient was discharged on a combination of Tridione, Phenurone, and thyroid. He was almost seizure-free and much more alert than on admission. However, the improvement did not persist. A psychologic examination later in the month showed definite evidence of organic mental deterioration.

On January 29, 1949 he was readmitted to the Children's Hospital after being lethargic for two days. He was dull and apathetic in appearance and deviated markedly to the right in walking. He spoke in a jargon due to a mixed receptive and motor aphasia and was thought to have a visual disturbance. There was a suggestive right central facial weakness and coordination of the right hand was poor. Tridione and Phenurone were stopped successively without change in his mental status and the spells returned. They recurred every few minutes and involved the right arm and leg in massive jerking movements. During intervals between seizures the right arm tended to be held rigidly in a flexion attitude. A right homonymous hemianopsia was first demonstrated on February 8, 1949. Serial electroencephalograms showed marked slow disorder (figure 1, D and E). Routine laboratory tests were normal. Lumbar puncture revealed initial pressure of 150 mm. The spinal fluid contained 1 lymphocyte per cu. mm. and 30 mg. per cent protein, 25 mg. per cent glucose, 122 meq./L. chlorides. Routine cultures of the spinal fluid were also negative. A pneumo-

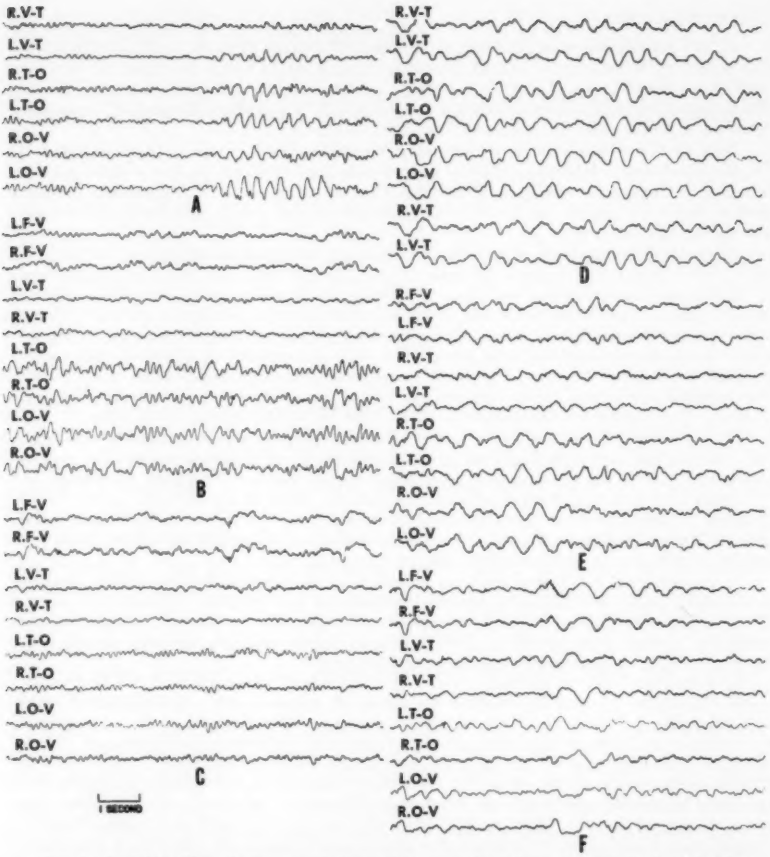

FIG. 1. Serial bipolar electroencephalographic recordings from patient N. A. (A) Initial record, March 24, 1948. Paroxysmal slow activity is seen in the posterior lead combinations, somewhat more prominently on the left. (B) July 29, 1948. The record is similar but somewhat more disordered than A. (C) Jan. 6, 1949. The record is generally better ordered than A and B. Paroxysmal slow activity is not seen. There was apparent clinical improvement at this time. (D) Feb. 3, 1949. There was clinical relapse and the record is grossly disordered with no evidence of focalization. (E) Feb. 19, 1949. Record remains disordered with sporadic evidence of a left posterior focal trend. (F) Feb. 1, 1951. Record remains generally disordered with bursts of irregular slow activity. F—frontal. V—vertex. T—temporal. O—occipital.

encephalogram was again interpreted as normal. Rectal temperature varied betwen 36.5° and 38.5° C. He weighed 65 pounds, 5 pounds less than a year before. After becoming progressively worse he was transferred to the neurology service at St. Louis City Hospital on February 22, 1949.

At this time the seizures consisted of a rapid ballistic flexion movement of the right arm,

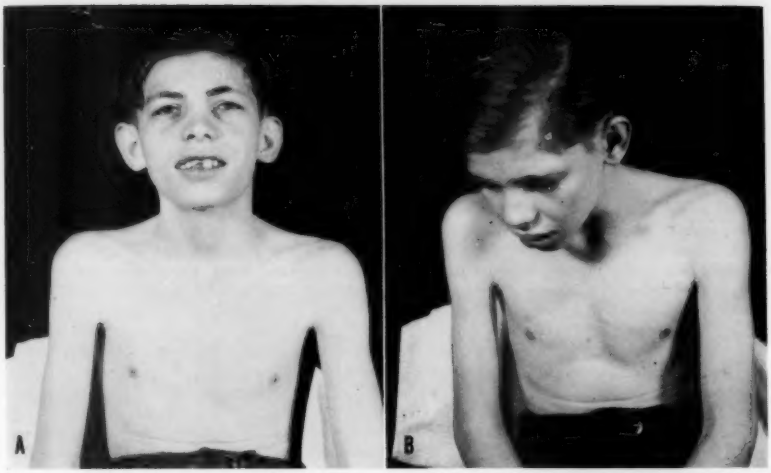

FIG. 2. Photographs preceding and during one of the residual seizures; taken March 1951. (A) Sitting at rest. (B) A moment later the head dips forward and to the right.

flexion-abduction of the right leg, a jerk of the right facial musculature and conjugate deviation of the eyes to the right with rebound to the left. The spells occurred every few minutes, became less frequent when he was drowsy, and were absent during sleep. He obeyed only the simplest commands, his speech was in disconnected syllables, and he did not appear to recognize his family. He was incontinent of urine and feces. Ballistic arm movements were so severe that the face and neck became contused and excoriated. The white blood cell count was 10,800 on admission; the remainder of the routine laboratory studies including those on spinal fluid were normal. Rectal temperatures ranged between 36.9° and 38.0° C. until March 25, 1949.

A left frontal exploratory operation was then undertaken with the combined purpose of obtaining a cortical biopsy and undercutting the arm area of the left hemisphere to reduce the violent right-sided movements. One sample of excised cortex was emulsified and inoculated intracerebrally into a monkey. The monkey was killed after he had remained asymptomatic for two months and histologic study did not reveal an encephalitic process. Another biopsy sample was prepared histologically and showed subacute encephalitis (see pathologic report). The immediate postoperative course was uneventful, but the jerking spells continued with unabated frequency and violence. The cerebrospinal fluid on March 31, 1949 was within normal limits, and culture in embryonated eggs was also negative.

On April 12, 1949 Aureomycin* 2 Gm./day was started. The temperature, hitherto in the same range as preoperatively, rose to 38.2° on April 13 and to 38.3° on April 15. This was attributed to a subcutaneous collection of sterile (bacteriologic culture) fluid at the operative site which was aspirated, the temperature returning to normal. The first course of Aureomycin was discontinued on April 26, 1949. Three days later the jerking movements were less severe, although they occurred as frequently as before. On May 18 the patient was brighter and more responsive and was eating well. The seizures were much less severe. Repeat lumbar puncture was again normal. By May 24 the child was still more alert, could count to 20, complete simple sentences, and recognize members of the hospital staff and of his family by name. He could walk with assistance. The temperature ranged between 36.0° and 37.0° degrees. Administration of Aureomycin was resumed on May 27, 1949. On May 31, he developed a fever of 38.5° with no apparent cause. The Aureomycin was

*Aureomycin was donated by Lederle Laboratories through the courtesy of Dr. Guy W. Clark.

continued through June 8, interrupted and then resumed between June 13 and June 20.

In the latter part of June further mental improvement was observed. The spells although less violent still prevented him from walking without assistance. By then bowel control was almost complete and bladder control was improving. The patient was discharged June 25, 1949, having received a total of 65 Gm. of Aureomycin.

Improvement has continued since discharge from the hospital. In April 1951 he was no longer incontinent, and was able to dress and undress himself slowly and help feed himself. A partial motor aphasia persists, but he is able to express clearly in short sentences all of his needs. He recalled the name of an examiner after not having seen him for several months. There is some perseveration in speech. The jerking movements occur from several seconds to a few minutes apart and have become reduced to a conjugate deviation of the eyes to the right usually associated with a dipping adversive movement of the head in the same direction (figure 2). Accompanying this is a slightly perceptible flexion of the right arm and stiffening in extension of the right leg and foot. There does not appear to be any loss of consciousness with these movements, nor do seizure discharges appear coincidentally in the electroencephalogram. However, brain activity remains grossly disordered (figure 1F).

The right arm is held in a hemiplegic posture and is somewhat spastic. A grasp reflex is present on the right, and there is a considerable deficit of strength and dexterity in movements of that arm. Tendon reflexes are generally hyperactive, slightly more so on the right, and there is an unsustained right ankle clonus. Plantar reflexes are flexor, the abdominal reflexes, active. Sensory examination is grossly normal. The right homonymous hemianopsia persists. The right optic disc is definitely pale. Visual acuity is normal by gross testing. He weighs 68 pounds.

Examination of serum in 1951 for complement fixation and neutralization for western equine and St. Louis encephalitis was negative. These tests were not available for use in the early stages of the illness.

SUMMARY OF CASE REPORT

A 10 year old boy developed mental deterioration insidiously and showed behavior difficulties. After a few months peculiar seizures appeared and for a time a brain tumor was suspected. Symptoms gradually progressed over the course of a year. Rapid acceleration of downhill course was manifested by signs of severe involvement of the dominant cerebral hemisphere. The diagnosis of subacute encephalitis was established at this time by cerebral biopsy. Associated with treatment by Aureomycin there was definite improvement which has continued during the period of almost two years since that antibiotic was administered.

PATHOLOGIC REPORT

DR. ROBERT L. LAM: A 2x2 cm. section of cortex and subcortical white matter was fixed in alcoholic sublimate and in formalin. Microscopic sections were stained with phosphotungstic acid haemotoxylin, hematoxylin and eosin, asure-eosin, Mallory trichrome, and Scharlach R.

There was marked evidence of subacute and chronic inflammation. Perivascular cuffing with lymphocytes (figure 3A) was prominent everywhere. The leptomeninges were moderately infiltrated by lymphocytes (figure 3B). The subcortical white matter had a spongy appearance and there was a small chronic glial scar showing retraction (figure 3C). Considerable glial proliferation was evident, particularly of microglia and astrocytes. Some of the latter showed marked hypertrophy (figure 3D).

In the cortex glial proliferation was also prominent and several glial nodules were observed (figure 3E). Chronic, subacute and acute stages of neuronal degeneration were

FIG. 3. (*opposite page*) Cerebral biopsy from patient presented here. See text of pathologic report above for details.

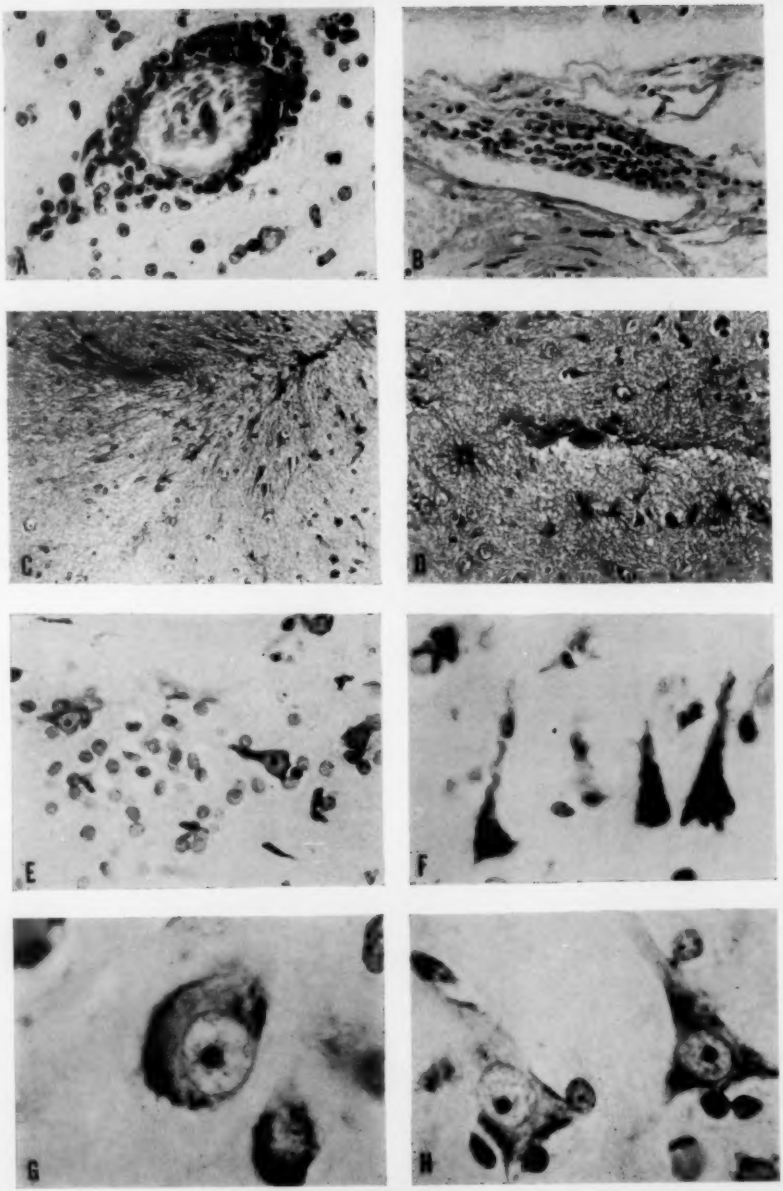

Figure 3.

particularly evident in the fifth and to a lesser degree in the third cortical layer (figure 3, F, G and H). Satellitosis was common (figure 1H). No inclusion bodies were observed.

COMMENT

The clinical and pathologic findings reported were strikingly similar to those in cases previously described as subacute inclusion body encephalitis[1] and subacute leucoencephalitis.[6] Thus even though inclusion bodies were not demonstrated in the limited biopsy material, there are no valid grounds for distinguishing our case from either group. This is particularly true since an infectious agent has never been isolated.

Evaluation of the possible role played by Aureomycin therapy in altering the progressive course of the disease must be based upon the observations by others on remission and survival in cases that were not so treated. Although most cases have progressed to death in a period of months, three cases in this country with inclusion have had considerably longer durations.* Cobb and Hill[10] mention an English patient proved by biopsy (no inclusions) who was still alive after two and a half years. There was a spontaneous partial remission of almost a year's duration. Dawson's first case began with an attack of unconsciousness 16 months before hospitalization.[1] There was progressive psychic change before the accelerated terminal course. The second and third cases of Malamud, Haymaker and Pinkerton[5] were ill one year and nine months and seven years, respectively. Partial remissions lasting for a few months are described in both patients.

Thus, in spite of the apparently continuous progressive course in the case reported here up to the time Aureomycin therapy was instituted, it is possible that a coincidental spontaneous remission may have occurred. The sustained clinical improvement since therapy suggests that Aureomycin played a significant role. Also suggestive that Aureomycin was effective were the transient febrile reactions which appeared with the first and second courses of the antibiotic. The first of these was attributed to collection of sterile fluid at the biopsy site. The febrile reaction with the second course was not related to any unusual circumstance.

Our failure to transmit the disease from biopsy tissue to one monkey is similar to that report by other workers. One of a variety of factors may account for these failures. Susceptibility of the host, or attenuation of the virus by prolonged contact with the cells of the donor brain are obvious ones, as is the limited number of animals used.

The electroencephalographic findings generally reflected the clinical course of the disease as it developed. Early in the course of the illness slow activity appeared paroxysmally and the record generally was not greatly disordered (figure 1, A and B). During one period of transient clinical improvement the record improved (figure 1 C). Somewhat later the record became generally

*Greenfield[4] has pointed out that there are some histologic differences between the cases reported by Brain, Greenfield and Russell[3] and those of longer duration reported by Malamud, Haymaker, and Pinkerton[5].

and severely disordered (figure 1, D and E), and these changes have persisted until this time (figure 1 F) in spite of clinical arrest of the deteriorative course and marked improvement in the status of the patient. Episodic slow waves became evident late in the course of the illness (figure 1 F). However, we have not been able to relate the involuntary movements to electroencephalographic activity.

SUMMARY

A case of subacute encephalitis in a 10 year old boy is described. The diagnosis was established by cortical biopsy done one and a half years after the onset of symptoms. The pathologic changes were similar to those of other cases of subacute encephalitis reported in the literature. No inclusion bodies were found.

Coincident with the administration of Aureomycin there was arrest of a rapid deteriorative course and remission has continued for two years since the antibiotic therapy was given. The significance of that therapy is discussed.

Serial electroencephalograms made during the course of the disease are described.

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Acknowledgment is made to Drs. G. Roulhac, S. A. Trufant, R. F. Schneider and D. Thurston for their contributions to this study. We are particularly indebted for the encouragement and advice of Dr. J. L. O'Leary. Dr. Robert L. Lam performed the pathologic study.

Effects of Cortisone in Myotonia Atrophica

Ralph W. Barris, M.D. and Harvey D. Strassman, M.D.

Neuromuscular disorders constitute a subclass of neurologic disorders which, as a group, remain somewhat obscure as to etiology or pathogenesis and which are not always strictly "neural" or strictly "muscular" in their clinical manifestations. This group of disorders is fairly heterogeneous, including such entities as the progressive muscular atrophies and dystrophies (or myopathies), myasthenia gravis and the myotonias. The myotonias are subdivided clinically into two main categories: 1) *myotonia congenita*, first described in 1876 by one whose family was afflicted with this disorder, Dr. Julius Thomsen,[1] and since that time often referred to as "Thomsen's disease"; and, 2) *myotonia atrophica*, first given this distinctive designation by Rossolimo[2] in 1902. This latter disorder is also sometimes referred to as myotonia dystrophica.

Since Hench and coworkers[3] first reported the beneficial effect of 17-hydroxy-11-dihydrocorticosterone (Compound E) in acute rheumatic fever, many additional studies have been undertaken to determine whether or not this substance, later referred to as cortisone, might be of value either as a therapeutic aid or experimental tool in other disease states, including most of the neuromuscular disorders. Not only has cortisone been employed in further study of these states, but pituitary adrenocorticotropic hormone (ACTH) has been employed in a similar fashion.

PRESENT STUDY

This paper deals with a study of the effect of cortisone in myotonia atrophica, together with a brief summary of the present status of ACTH and cor-

From the department of medicine (neurology), University of California School of Medicine, Los Angeles, California, and the neurology section of the medical service, Wadsworth Hospital, Veterans Administration, Los Angeles, California.

Reviewed in the Veterans Administration for publication with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

tisone in the neuromuscular disorders. It seems desirable to review briefly the clinical signs and symptoms of myotonia atrophica, and return later to some of the more outstanding metabolic features of the disease, as well as to considerations of the influence of cortisone on chemical alterations of the blood and urine and on the myotonic reactions.

Myotonia atrophica is a progressive disorder of unknown etiology, the signs or symptoms of which usually appear for the first time in the third decade. Occasional cases, however, have been reported as first appearing in late juvenile years, and others in the fourth, fifth or even sixth decades. Its onset is insidious, as a rule, usually beginning with premature frontal baldness. In time the first signs of myotonia appear, chiefly noted by the patient when he finds himself unable to "let go" of objects grasped in his hand. This myotonic reaction has a predilection for certain muscle groups, chiefly the flexors and extensors of the wrist, hand and fingers, the adductors of the thumbs, the tongue musculature, and the deltoid and peroneal groups. Males are much more commonly affected than females, and cases occur more often in a sporadic fashion than in relationship to a heredo-familial background. In the course of years there is progressive atrophy of muscles, eventually quite generalized, but with an especial early predilection for the temporo-masseter muscles, bulbar (palato-pharyngeal) muscles, the muscles of facial expression, the sternocleido-mastoid and other neck muscles, as well as for the peroneal muscle groups of the lower extremities and to a lesser degree the distal musculature of forearms and hands. This muscle atrophy is associated with a progressive impairment of motor activities, the gait becoming feeble, often of the "steppage type," and the facies taking on the characteristics of this disorder. As atrophy of the bulbar muscles ensues, speech becomes weak and swallowing is often impaired. Incidental but important findings include in most cases the existence of premature cataracts, with associated reduced visual acuity and later amaurosis, a sparseness of hair of the beard, and of the axillary and pubic regions. Testicular or ovarian atrophy is evident almost universally. After many years, these individuals may reach a stage of invalidism requiring a wheel chair, or eventually assume a bed-ridden status.

PREVIOUS STUDIES

There have been several reports during the past three years relating to results of ACTH and cortisone therapy in many of the neuromuscular disorders.[4–9] To date, except for the possible therapeutic benefit of ACTH in myasthenia gravis,[7,9] past studies have shown that ACTH is of doubtful value as a therapeutic agent in the treatment of neuromuscular disorders. Cortisone, however, although of questionable benefit in most of the neuromuscular disorders, has been shown by Shy and coworkers[8] to have favorably influenced the myotonic reaction in two cases of myotonia atrophica.

EFFECT OF CORTISONE ON MYOTONIC REACTIONS

In the present study, cortisone acetate (100-250 mg. daily) was administered orally or intramuscularly to each of six adults with myotonia atrophica.

TABLE 1

EFFECT OF CORTISONE IN MYOTONIA DYSTROPHICA

INFLUENCE ON MYOTONIA

Case	*Age*	*Sex*	*Duration of Disorder*	*Daily Dose Cortisone (mg.)*	*Mode of Administration*	*Days of Treatment*	*Result*
1	54	0	27 years	100–200	I.M.**	21	Improved
2	56	0	21 years	100–200	I.M.**	21	Improved
3	36	0	9 years	200–250	I.M.**	22	Improved
4	31	0	7 years	200	Oral*	24	Improved
5	27	0	11 years	200	Oral*	15	Improved
6	59	0	34 years	200	Oral*	15	Improved

*Liquid suspension, cortisone acetate with vehicle (raspberry syrup).

**All dosages given b.i.d., at 12 hour intervals.

Beginning at the seventh or eighth day following therapy, a decrease in the time required for relaxation of muscles exhibiting the myotonic reaction was noted.

Cortisone was administered for periods ranging between 15 and 22 days, the average being 21 days, after which it was discontinued. Within 72 hours after discontinuance of the drug, the myotonic reactions as revealed by thenar percussion, forearm percussion, and opening and closing of the hands, resumed the status observed prior to therapy (table 1).

It should be mentioned that in only one of the six cases was there evidence of a heredo-familial background to the disorder. In this instance a paternal cousin, aunt and two uncles were similarly afflicted.

EFFECT OF CORTISONE ON METABOLIC ACTIVITIES

Prior to, during and after cortisone therapy, frequent estimates were made of the blood serum levels of sodium, potassium, cholesterol, cholesterol esters, creatine and glucose. Alterations in the levels of these substances were not significant.

The urinary excretion of creatinine was somewhat equivocal but in general tended to be lower after the first week of cortisone therapy than before that time. Additional observations are being carried out to further clarify this.

17-Ketosteroid excretion. The level of neutral urinary 17-ketosteroids is considered to be an index of the elaboration of androgenic hormone by the adrenal cortex in the female, and by the adrenal cortex and testicles in the male. There is excreted by normal men per 24 hours (Caughey and Brown[10]) an amount ranging between 7 mg. and 17 mg. It is important to note that in the present series of 6 cases, all males, the 24 hour excretion of 17-ketosteroids ranged between 4.4 mg. and 8.1 mg., an average of 5.1 mg. daily. Caughey and Brown[10] have recently reported that in nine cases of myotonia atrophica the 24 hour urinary excretion of 17-ketosteroids ranged between 1.0 mg. and 5.5 mg., with an average excretion of 2.8 mg. In another series of five cases

reported by Benda and Bixby,[11] the daily output ranged between 2.8 mg. and 8.0 mg., with an average of 5.5 mg. Thus, the present findings of a low average daily output of 17-ketosteroids in myotonia atrophica is comparable to the results of other workers. Of great interest was the observation that however low the normal excretion of 17-ketosteroids might be prior to cortisone therapy, this excretion was decreased still further following administration of the hormone. Following cessation of therapy, the 17-ketosteroid excretion resumed its pre-cortisone level. This observation of reduced 17-ketosteroid excretion during cortisone therapy in patients with rheumatoid arthritis has been previously noted by Hench et al.[12] and by Sprague et al.,[13] and thought to reflect a reduced level of adrenal cortical and/or testicular hormonal function.

Additional observations: In four of six patients increased growth of hair was noted in scalp, face and chest areas. All patients affected were aware of this change and were usually the first to call attention to it. Increased facial hirsutism during cortisone therapy has previously been reported by Sprague and associates,[13] and hypertrichosis was reported by Boland and Headley[14] in seven of 24 cortisone-treated cases of rheumatoid arthritis. Most of the patients reported an increased sense of well-being and felt less fatigued on walking and in other motor activities.

SUMMARY AND CONCLUSIONS

1. Cortisone acetate has been administered orally and intramuscularly to six cases of myotonia atrophica in daily doses of 100 to 250 mg.

2. During cortisone therapy there was noted a reduction in the myotonic contraction of muscles, a decreased 24 hour urinary excretion of 17-ketosteroids, and a fall in urinary creatinine excretion.

3. Incidental observations include increased growth of scalp, facial and body hair, and increased sense of well-being.

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It is necessary, in speaking of the functions of the brain, to use the term "centre." Remember that the word is employed in its physiological sense; not in a geometrical, or even in a topographical, sense. It indicates a combination of nerve-cells subserving a given function. Note, first, that this function may not be the only one subserved by the group of nerve-cells. In many groups the nerve-cells are very numerous; they are connected with each other by a ramifying plexus of fibrillae, and are connected with other and distant groups of cells by nerve-fibres. Such a collection of cells may contain many centres, since only some cells are probably in action at the same time. The possible functional combinations in such a group are almost infinite, since the variations involve not only the number of cells in action, but the relative degree of their action. Only some of these are usually, perhaps ever, in functional activity. Lines of various resistance exist by which the functional combinations are determined. Education is largely the establishment of these lines of least resistance. Habit depends upon them. Although the finest, most complex mechanism of human contrivance is rude compared with the simplest arrangement of the brain, I may illustrate this variation of function by an object with which you are all familiar. Wherever large buildings are being erected, or extensive excavations made, you will see a steam crane. This machine, by a change in the relation of the different parts of the complex mechanism, may be made either to draw up a weight, to swing itself round, or to travel along a line of rails. The motive force is the same—the machinery is essentially the same; the difference in result depends on certain parts of the machinery being in or out of "gear". In the one machine are functional centres for progression, rotation and turning a windlass.

—Sir William R. Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord*, published in 1885.

Extinction Phenomenon in Patients With Verified Cerebral Tumors

Dewey K. Ziegler, M.D.

WITHIN recent years Bender and his associates have brought to the attention of neurologists the value of using simultaneous bilateral stimuli and other double stimuli in the testing of cutaneous sensation, and have demonstrated the frequency of patients' imperception of one stimulus when such methods are utilized.[1–4] This phenomenon of imperception of one of a pair of widely separated stimuli, in the presence of comparatively normal sensation under orthodox single stimulus testing, Bender has termed "extinction." It has been demonstrated in patients with lesions in various parts of the neuraxis.[1,2] Bender's original patients were, for the most part, those with intracranial injuries in the parietal area, but he has since demonstrated extinction in a large percentage of patients with cerebrovascular accidents affecting other portions of the cerebral hemispheres. Interest has centered chiefly in the psychological significance of the extinction phenomenon in relation to space perception, and in general, to the over-all patterning of sensation, normal and abnormal; the cases recently studied have been mostly those of diffuse brain disease.[3–6]

It occurred to the author that it would be valuable to determine the significance of occurrence of the extinction phenomenon in patients with cerebral tumors. If, for example, the extinction phenomenon were a fairly specific sign of parietal lobe lesions, the usefulness of routine testing for extinction would be validated. Patients to be operated on for intracranial masses (chiefly neoplasms) provided the opportunity to study this question.

The main purpose of the present study was to determine the incidence of the extinction phenomenon in patients with space-occupying lesions in different areas of the cerebral hemispheres and to study how this phenomenon correlates with the presence or absence of the more commonly recognized signs of cortical sensory deficit. Other questions investigated were the relative efficacy of pain versus touch stimuli in evocation of the extinction phenomenon, the importance of simultaneous stimulation of heterologous areas

From the Neurological Institute and the department of neurology, College of Physicians and Surgeons, Columbia University, New York City.

(as opposed to homologous areas), and the effect of increased intracranial pressure as a factor in the occurrence of extinction.

Recently Cohn[7,8] and Bender[9] have established the fact that when separated simultaneous stimuli are applied to the same side of the body (the side with the impaired sensation) frequently only one of these stimuli will be perceived. There is, according to Cohn, a definite pattern in these patients of rostrocaudal dominance to the stimuli perceived and those not perceived. The presence or absence of such a pattern was looked for in these patients.

CASE MATERIAL

A series of patients who were diagnosed from the history and physical findings as having a mass lesion in one of the cerebral hemispheres, were examined preoperatively. No patient was included who was considered too drowsy, confused or aphasic to give comprehensible and consistent answers. Only those cases will be analyzed here in which the existence and location of the lesions were confirmed by operation or by air study. There were 34 such cases, in 29 of which location of the lesion was confirmed by air study and subsequent operation, and in five by air study alone.

PROCEDURE

All patients were given a complete neurologic examination. Pain perception was tested with 5 gram stimuli on calibrated spring algesiometers, and pressure sensation with 25 gram nylon "Von Frey hairs." Each patient was tested for the extinction phenomenon with simultaneous application, first with algesiometer stimuli, to the following areas: 1) bilaterally homologous areas of the body – face, shoulders, volar aspects of the wrists, hips, dorsa of the feet; 2) heterologous areas of the body – left wrist and right foot, right wrist and left foot; 3) areas on the same side of the body – face and shoulder, face and hand, shoulder and hand, shoulder and hip, hip and foot.

The whole procedure was then repeated, using the 25 gram "Von Frey hairs" as non-painful stimuli. The patients were tested repeatedly until the pattern of their responses became evident.

RESULTS

Patients Showing No Extinction

Twelve of the 34 patients (35 per cent) showed no extinction phenomena when tested as above. Five of these patients had frontal tumors, of which three were deep frontal gliomas extending back to the region of the motor strip, one was a large frontal convexity meningioma, and another a large deep angioma. There was one comparatively superficial parasagittal meningioma extending across the midline in the area of the motor strip. The other tumors were: one sphenoid ridge meningioma, one anterior corpus callosum tumor, one temporal lobe tumor, and two deep temporoparietal masses (table 1).

Six of the 12 patients had increased intracranial pressure, with demonstrated shift of the ventricular system to one side. Five had a history of

TABLE 1

LOCATION OF TUMORS IN PATIENTS SHOWING NO EXTINCTION PHENOMENA

Frontal	5
Deep gliomas	3
Convexity meningioma	1
Angioma	1
Parasagittal (meningioma)	1
Sphenoid ridge (meningioma)	1
Suprasellar (meningioma)	1
Corpus callosum (anterior)	1
Temporal	1
Temporoparietal	2
Total	12

TABLE 2

LOCATION OF TUMORS IN PATIENTS SHOWING EXTINCTION PHENOMENA

Parietal	14
Parasagittal (meningiomata)	5
Fronto-parietal	4
Posterior parietal	5
Frontal (all deep, posterior frontal)	4
Temporal	2
Intraventricular (III and lateral)	1
Posterior fossa (acoustic neurinoma)	1
Total	22

unilateral sensory symptoms presumably ascribable to their lesions—such as feelings of numbness, tingling, and "electricity" in one extremity. Three gave no extinction phenomena, but showed other signs of cortical sensory deficit, such as loss of position sense in an extremity, astereognosis, or defective perception of palm writing.

Patients Showing Extinction Phenomena

Twenty-two of these 34 patients (65 per cent) showed some form of extinction phenomena. In 16 patients extinction phenomena could be obtained by stimulating homologous areas of the body bilaterally. In 11 of these, the phenomenon occurred when either pain or pressure were used; in the other five it occurred only with the pressure stimulus and not with pain. In two patients stimulation of non-homologous areas bilaterally was the only method by which extinction could be elicited. Three patients showed extinction only when the unilateral simultaneous stimulation was used, and one on bilateral pressure stimuli reported a feeling of continuation of the stimulus on one side after it had been removed; this was not true extinction, but was felt to be an allied phenomenon.

Of the 22 patients, 13 showed increased intracranial pressure, and, in most cases, a shift of the ventricular system to one side. Nine showed no indication of increased pressure.

Location of lesions in patients showing extinction: Fourteen patients had predominantly parietal lesions of the following varieties: five parasagittal meningiomas, four anterior parietal or fronto-parietal lesions, four posterior parietal lesions (three cysts and one angioma). There were four frontal lesions, all posterior frontal and deep gliomas, of which two were definitely noted to extend behind the central fissure, and a third was thought probably to do so. There were two preponderantly temporal lesions, both of which were large, extending subcortically out of the temporal lobe, and one case of intraventricular tumor extending from the third ventricle into the lateral ventricle, and one case of posterior fossa tumor (table 2).

There were nine predominantly right sided lesions and 11 left sided lesions, with one posterior fossa tumor and one falx meningioma. When the testing clearly and consistently produced extinction on one side of the body, the lesion

was always in the contralateral cerebral hemisphere.

Sensory signs and symptoms in patients showing extinction: Of the 22 patients showing extinction, 14 had had sensory symptoms of the type described above—namely, numbness, tingling, or feelings of "electricity"—while eight had had none.

Twelve of the 22 patients showed on examination unilateral cortical sensory loss, two were not adequately examined to be evaluated, and eight showed no such signs. The latter eight were considered to be of some interest, and further breakdown disclosed that two of these patients showed extinction responses only on stimulation of heterologous areas, two only on rostrocaudal unilateral stimulation, and four only when a pressure stimulus, instead of a pain stimulus, was used. In two of these eight patients the extinction phenomenon appeared inconstantly and bilaterally. One of the eight had a posterior fossa lesion.

Unilateral stimuli-rostrocaudal dominance: All patients who showed extinction phenomena of any kind, except one, and two who were not examined, also demonstrated some degree of rostrocaudal dominance or extinction when simultaneous stimuli were applied to two areas on the same side of the body. All of these patients except two showed this phenomenon when either pain or pressure was used. In the two in whom it appeared only with pressure stimuli, the responses were bilateral, varying and difficult to assess.

The patterns of extinction appearing in these patients showed that the face was fairly consistently dominant over the shoulder, wrist, hip and foot. Even in patients who showed no other extinction phenomena, the face stimulus often extinguished the shoulder bilaterally. Usually the shoulder and upper arm extinguished the wrist and hand. Usually, also, but with many exceptions, the hip was dominant over the ankle and dorsum of the foot. It was impossible to find in this series any regular dominance displayed between hip and shoulder stimuli, or between hand and foot; at one time the one, at one time the other, appeared dominant, alternating frequently in the same patient.

"Well-defined" versus "slight" extinction: It was noted that some patients showed the extinction phenomenon on every application of stimuli. In these patients unilateral extinction tended to occur in a consistent pattern. Other patients, though showing definite extinction phenomena, did so only a certain proportion of the times the stimuli were applied. In these patients rostrocaudal extinction was occasionally displayed bilaterally and in a pattern that showed variation from time to time and was discerned only by dint of repeated testing. The latter group was said to show extinction of a "slight" degree, the former, "well-defined." The location of lesions giving well-defined extinction was as follows: four posterior parietal lesions (tumors and cysts), three frontal tumors (deep posterior frontal gliomas), one parietal "gliosis," one temporoparietal tumor, and one parasagittal meningioma. Lesions producing slight extinction were as follows: five parasagittal tumors (meningio-

TABLE 3

OVER-ALL OCCURRENCE OF THE EXTINCTION PHENOMENON AS CORRELATED WITH LOCATION OF TUMORS

Location of Lesion	*Number of Cases*	*Well-Defined*	*Extinction Phenomenon (Number of Cases)* *Slight*	*Absent*
Frontal lobe	9	3	1	5
Parietal lobe	7	5	2	0
Temporoparietal	3	1	0	2
Parasagittal	7	1	5	1
Temporal lobe	3	0	2	1
Posterior fossa	1		1	
Intraventricular	1		1	
Corpus callosum (anterior)	1			1
Sphenoid ridge	1			1
Suprasellar	1			1
Total	34	10	12	12

mas), two parietal tumors (angiomas), two temporal tumors, one deep frontal tumor, one posterior fossa, and one intraventricular tumor.

Of the ten patients showing well-defined extinction, nine had other cortical sensory signs, one did not. Of the 12 patients showing slight extinction, five showed other cortical sensory signs, seven did not.

In table 3 the over-all incidence of the extinction phenomenon, both slight and well-defined, as found in patients with tumors of the different parts of the cerebrum, is recorded.

Other findings: Several patients who displayed extinction with bilateral stimulation also displayed the "displacement" phenomenon in which one stimulus (on the affected side) was felt at a point distant from its application. Displacement in the extremities was almost uniformly proximal, i. e., the stimulus from the foot was felt in the thigh or hip, that from the hand in the shoulder. Although some shoulder and arm stimuli were referred to the face, on occasion face stimuli were also displaced to the shoulder.

When rostrocaudal dominance was being tested with simultaneous unilateral stimuli, three types of displacement phenomena were occasionally noted on the affected side. A few patients felt one stimulus midway between the two applied; a few others reported one of the stimuli in a different extremity, but on the same side; for example, one patient given hip and foot stimuli reported sensation in the ipsilateral hip and hand. Occasionally a patient displaced one stimulus to the homologous extremity on the unaffected side.

Two patients in the series had severe spontaneous pain in an affected extremity as a prominent symptom. Both of these patients had mid-parietal tumors extending deep into the subcortical white matter of the parietal lobe.

COMMENT

The difficulty in trying to correlate clinical signs with location of brain tumors is noteworthy for several reasons. The possibility that a sign can be ascribed to increased intracranial pressure must first be considered. In this series six out of 12 patients who did not show extinction, and 13 out of 22

who did, had increased intracranial pressure. The latter factor would then appear to be negligible in itself in the production of the extinction phenomenon.

It is difficult also, even at autopsy, to gauge the actual extent of many intracranial tumors, particularly the gliomas, and therefore only gross correlations of tumor location with clinical signs can be made. With this reservation in mind, however, certain facts about the location of lesions producing extinction phenomena are suggested by the data given here.

It has been thought that the extinction phenomenon was a sign of parietal lobe disease,[1,2] and this hypothesis is borne out by the data presented here; 14 of the 22 cases showing extinction had parietal lesions. It is noteworthy, however, that the extinction phenomenon is not universally demonstrable in parietal lobe disease; two cases of parietal lobe tumor showing other sensory signs did not show extinction.

Of the patients with predominantly frontal lesions, five did not display extinction phenomena and four did. Three of the latter, however, were tumors suspected of invading the parietal lobe. It appears, therefore, that frontal lesions rarely give rise to the extinction phenomenon unless they extend posteriorly to the parietal area. Extinction phenomena were occasionally found in patients with tumors in a variety of other locations—temporal lobe, intraventricular, posterior fossa—and the localizing value of the sign is therefore limited.

Extinction phenomena were produced as commonly by lesions of one hemisphere as by those in the other; when clearly indicating one side of the body, it was never a false localizing sign, but was always produced by a lesion in the contralateral cerebral hemisphere. This point is made because certain disorders of perception, notably anosognosia, have been correlated with lesions of the minor hemisphere.[10] It may be remarked parenthetically, that although anosognosia was not routinely checked and tabulated, it was observed in only a few of these cases. This may well be because anosognosia is more readily produced by the rapid destruction of a massive area of brain, which occurs in a vascular lesion, than by the more gradual damage inflicted by a tumor, which permits greater adaptation and substitution of function by other regions.

Three points of importance in regard to the technique of examining for extinction are: the value of (1) repeated testing, (2) varying the area tested, and (3) varying the type of stimuli used. It was frequently found in these patients that repeated application of stimuli demonstrated extinction a certain percentage of the time, whereas a single application might reveal none.

Bender has recently pointed out the value of testing non-homologous areas for extinction,[4] and the usefulness of this modification was confirmed in the present study. It was found also that the use of a light pressure stimulus elicits extinction in several patients where the painful stimulus does not. Rarely extinction was obtained only on rostrocaudal testing, but in these

cases the results were often equivocal.

It is interesting to note that while the extinction phenomenon is usually found in patients with evidence of other cortical sensory deficit, it is not always present in such cases, and it also occurs in the absence of such deficit. The latter fact is illustrated by eight patients of this series. In these eight it was necessary to elicit extinction with the various modifications of the test described above.

Correlation of location of tumors with the kind of responses given suggested an interesting contrast. Well-defined and consistent unilateral extinction phenomenon was always produced by deep-seated lesions, usually exclusively parietal. In all but one case extinction phenomenon was accompanied by other sensory signs. The more evanescent, difficult to elicit, and occasionally bilateral extinction phenomenon was found usually in superficial lesions—parasagittal meningiomas and angiomas—and occasionally with lesions at some distance from the parietal lobe. In over half these cases extinction was the only sensory sign found. In some cases it was a clue to the location of the lesion, but in a few it was misleading.

The pattern of unilateral rostrocaudal dominance found in these patients is roughly similar to those recently described in detail by Cohn[7] and Bender,[9] the general rule being that the more proximal part of the extremity dominated the distal, with the face dominating all. The various patterns of displacement of stimuli found also follow patterns recently discussed by Bender.[11]

SUMMARY AND CONCLUSIONS

Thirty-four patients in whom the clinical diagnosis was cerebral hemisphere tumor, and whose lesions were later confirmed by operation or air study, were examined preoperatively for the presence and pattern of the extinction phenomenon. The following conclusions are made from these examinations.

1. The extinction phenomenon was usually found to be a sign of parietal lobe lesions, but it occurred occasionally in patients with deep frontal lesions and rarely was a manifestation of lesions in other locations, usually adjacent to the parietal lobe.

2. A few patients with parietal lobe lesions who show other signs of "cortical sensory" deficit, fail to show extinction (two cases).

3. Increased intracranial pressure and the side of the lesion have no influence on the presence or absence of the extinction phenomenon.

4. The use of simultaneous light pressure stimuli, simultaneous testing of non-homologous areas, and repeated testing was found to be the most effective way to elicit extinction.

5. Some degree of extinction phenomenon on testing with unilateral simultaneous stimuli was found in almost all patients who showed any other kind of extinction. The fairly constant patterns observed were the dominance of the face over the rest of the body, and of the proximal over the distal parts of the extremities.

6. Extinction phenomenon is occasionally present in patients who have no history of sensory disturbances and in patients who show no other signs of sensory deficit.

7. Consistent and "well-defined" extinction phenomenon must be differentiated from "slight" and inconstant extinction. The former was always produced by deep-seated lesions, usually in the parietal lobe; the latter usually by superficial frontoparietal lesions, notably the parasagittal meningiomas, but occasionally by lesions at a distance from the parietal lobe.

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The author's present address is Boston Psychopathic Hospital, Boston, Massachusetts.

The question may perhaps have occurred to you—Is there any relation between the seat of pain and the position of the lesion? All that can be said is, that there is sometimes no correspondence, sometimes there is a general correspondence, and occasionally there is a close correspondence. Pain at one part of the skull is rarely caused by disease at an opposite part of the brain; one-sided pain is usually due to disease on that side; disease beneath the tentorium generally causes pain at the occiput, which may pass down the neck; and disease at the surface of the brain often causes pain corresponding closely to the seat of the lesion. Light percussion sometimes elicits tenderness over the seat of the disease—pain being produced by a tap there, and not elsewhere. This is most frequently the case when the disease is superficial. The relation of pain to the nature of the lesion we shall consider in a subsequent lecture.

—Sir William Gowers in *Diagnosis of Diseases of the Brain and of the Spinal Cord,* published in 1885.

Double Simultaneous Stimulation Phenomena in Spinal Cord Disease

Mortimer F. Shapiro, M.D. and Daniel S. Feldman, M.D.

DOUBLE simultaneous stimulation (D.S.S.) phenomena are the patterned alterations in the perception of one stimulus when another is simultaneously presented to a different region in the sensory field. These alterations include extinction, obscuration, displacement and exosomesthesia. Thus, when a single pin prick is applied in a given area it may be well perceived; when applied simultaneously with another stimulus elsewhere the patient may fail to "feel" it (extinction); it may be dulled (obscuration); felt elsewhere on the body (displacement); or mislocalized to extra-personal space (exosomesthesia). Double simultaneous stimulation phenomena have been observed with cutaneous, proprioceptive, visual, auditory and gustatory stimuli in individuals with cerebral lesions.[1-7] The consistent manifestation of one or more of these phenomena in an adult indicates the presence of disease of the central sensory pathways, or an overall disturbance in brain function.

In the studies of double simultaneous stimulation phenomena previously reported there has been little information presented about their relation to diseases of the spinal cord. Bender states that the method of double simultaneous stimulation demonstrates alterations in sensibility in "some (patients) with lesions of the spinal cord . . .,"[8] but gives no indication of the incidence or types of these alterations. The present study was undertaken to assess the frequency with which less sentient areas could be demonstrated by this means, the pattern of altered sensibility, and the value of the method of double simultaneous stimulation in the diagnosis and localization of lesions of the spinal cord. The study was limited to patients in whom the disease process was confined anatomically to the spinal cord.

METHOD

Patients with spinal cord disease were studied at the Bellevue Psychiatric and Mount Sinai Hospitals. In addition to the routine neurologic examina-

From the neurologic service of The Mount Sinai Hospital and Bellevue Hospital, New York City.

Read at the fourth annual meeting of the American Academy of Neurology, Louisville, Kentucky, April 24, 1952.

tion methods, double simultaneous stimulation techniques were used. The patient was asked to close his eyes. A cutaneous stimulus, such as touch, rubbing, pin prick or vibration,* was applied to an area known or presumed to be above the radicular level of the cord lesion. At the same time a second cutaneous stimulus was applied to an area below the presumed level. This lower area had previously been reported by the patient as sentient to some degree on routine single stimulus examination. The patient was asked to report what he felt and to indicate where he felt it. If the upper stimulus was the only one perceived, additional trials were made, simultaneously stimulating the same upper area and successively more rostral portions of the lower area so that the level was approached with the lower stimulus. Patients were instructed to state the location, quality and intensity of the two stimuli. The level at which the subject reported the lower stimulus as being of an intesity equal to the upper and where both were correctly localized was termed the level to double simultaneous stimulation.

RESULTS AND CONCLUSIONS

Frequency of double simultaneous stimulation phenomena: Of the 50 patients in this series, double simultaneous stimulation phenomena were elicited with regularity in 24, an incidence of 48 per cent. This is distinctly lower than the incidence of 88 per cent reported in focal cerebral disease (hemiplegia) by Bender and his colleagues.[2] In this study no relationship could be demonstrated between the incidence of such phenomena and the type of spinal cord disease.

Double simultaneous stimulation phenomena when single stimulus examination is normal: Patients with cerebral disease in Bender's series frequently showed extinction when no sensory deficit was apparent on single stimulus examination. Although the same phenomenon has been observed in this study of spinal cord disease, it is an uncommon one. Of the 50 patients studied only two showed a sensory deficit to double simultaneous stimulation when none was elicited on single stimulus examination. However, when consistent extinction is seen, as in the case reported below, it is indicative of organic disease. Such phenomena may presage the later appearance of sensory disturbances to single stimuli and a double simultaneous stimulation level may accurately disclose the anatomic level of a lesion.

A 65 year old housewife had increasing pain in the left scapular region for a seven week period prior to admission to the hospital. The pain was aggravated by coughing and change of position and radiated into the lower chest. On examination she had an ataxic, broad-based gait. The Romberg sign was present. There was slight tenderness to the left of the midthoracic vertebrae. The sensory examination with single stimuli and by the method of double simultaneous stimulation was normal. X-rays of the spine were normal. Lumbar puncture on admission showed a partial block on jugular compression and a protein of 57 mgm. per cent. The lumbar puncture was repeated four days later. At that time a complete block was present and the cerebrospinal fluid protein was 154 mg. per cent.

*Vibration stimuli are included for our purposes in the term "cutaneous" since in their administration a true cutaneous stimulus must always be given.

Five or six hours after the second puncture localizing phenomena appeared for the first time in the form of a sensory defect evident only on double simultaneous stimulation examination, which disclosed a level at the T_3 dermatome, with extinction of pin or rubbing stimuli below when simultaneous face or neck stimulation of a similar sort was applied. Although double simultaneous stimulus examination consistently demonstrated this level, single stimulus examination at this time was still within normal limits.

The following day myelography showed a blocking lesion at the upper border of the T_4 vertebral body. Re-examination after the myelogram again disclosed a clearly defined double simultaneous stimulation level (with extinction below) at T_3, and for the first time some evidence of sensory deficit on single stimulus examination. Only on the following day could a clinically valid sensory level be elicited by single stimulus methods. Operation showed an epidural tumor at the level of the third and fourth thoracic vertebrae.

Types of double simultaneous stimulation phenomena: Extinction, obscuration and displacement were observed in this series of patients. As in cases of cerebral disease, extinction and obscuration were common. However, in contrast with cases of disease of the brain,[9] patterned mislocalization of one of the percepts (displacement) was only rarely observed when the disease process was limited to the spinal cord. The following case, however, illustrates the pattern of this phenomenon under these conditions.*

A 43 year old man complained of progressive numbness and weakness of the left lower extremity for eight months. At the age of 29, following trauma, a mid-thigh amputation had been performed on the right lower extremity. Examination showed paresis of the left lower limb and the stump of the right. Pain, temperature and vibration sensibility (tested with single stimuli) were diminished below the level of the fourth thoracic dermatome. Double simultaneous stimulation examination, one stimulus applied above the T_4 dermatome at the same time as another was simultaneously applied below, usually elicited either extinction or displacement of the lower stimulus. When displacement was found he reported feeling two sensations near the area of the upper stimulus. Thus when a pin was applied to the left cheek and a vibrating tuning fork placed on the left ninth rib at the same time, he reported feeling a "stick and a buzz" on the left cheek. If a tuning fork was applied to the forehead and his left ankle was simultaneously pricked with a pin, he reported a "stick and a buzz" on the forehead. The displacement or mislocalization always occurred to the site of the upper stimulus. Noteworthy in this case was the fact that these phenomena could be obtained even when the patient observed the application of the stimuli.

Exosomesthesia is a rare displacement phenomenon sometimes seen in cerebral disease.[10] The term is applied to the patterned or systematized mislocalization of a sensory percept into extra-personal space. It is usually elicited only under the condition of double simultaneous stimulation. In our series where the disease process was limited anatomically to the spinal cord exosomesthesia was never observed.

Effect of dissimilar stimuli: Studies on patients with cerebral disease have shown that double simultaneous stimulation phenomena may be elicited when the two stimuli which are simultaneously applied are of differing types. By way of example, a vibrating stimulus (tuning fork) may extinguish the perception of pin prick, or light touch to the face cause extinction, obscuration or displacement of a painful stimulus simultaneously applied to a different area. These phenomena were observed to occur frequently in this study of patients with spinal cord disease. However, such phenomena were more

*This case has been reported in greater detail by Morris B. Bender.[1] Through the courtesy of Dr. Bender we were permitted to examine this patient.

easily elicited when the two stimuli were similar, and in no individual in whom they could be demonstrated with dissimilar stimuli were they absent when the simultaneously applied stimuli were the same.

Role of the face: Under the conditions of double simultaneous testing, stimulation of the face was the technique most likely to produce alterations in the perception of the lower stimulus. In some patients the phenomena could not be demonstrated unless the face was one of the two areas simultaneously tested. Moreover, there was no instance in which stimulation of any area above the lesion produced extinction, obscuration or displacement of the lower stimulus and stimulation of the face failed to do so. There was no case in which the lower stimulus affected the perception of that applied to the face. These findings parallel those of other studies of double simultaneous stimulation phenomena.[1,2] They demonstrate again that in the sensory hierarchy of the body, the face is the most dominant area.

Value of double simultaneous stimulation study of cord disease: Double simultaneous stimulation examination techniques appear to be of value in the examination of patients with spinal cord disease. Although it is not common for a level to be evident on double stimulation when single stimulation examination is normal, sensory changes of localizing value sometimes occur under these conditions alone, and presage the appearance of a level with single stimuli. Double simultaneous stimulation levels are usually clear-cut and sharp; the patient does not have to effect a comparison between two successive stimuli but only needs report whether he feels one or two stimuli.

The finding of extinction is often of great value in the examination of psychotic or confused individuals. In one case a psychotic, uncooperative patient gave responses on single stimulus examination which were bizarre and contradictory. When double stimulus examination techniques were used and the patient urged to brush away any painful stimuli he felt, a consistent level was easily demonstrated.

Levels elicited by this method coincide with the anatomic level of the pathologic process in the spinal cord as accurately as do those elicited by single stimulation methods. In no case in which a level could be shown by double and single stimulation were the results markedly disparate. In the two patients in whom a level could be obtained only by double stimulation it coincided accurately with the anatomic level of disease.

No conclusions as to the underlying mechanism of double simultaneous stimulation phenomena can be drawn from this study. These findings, however, do serve again to demonstrate the interaction between two stimuli simultaneously presented. They demonstrate that double simultaneous stimulation phenomena can be found when there is disease of the sensory pathways in the spinal cord, and that these phenomena are clinically valuable.

SUMMARY

1. Double simultaneous stimulation phenomena were observed in 24 of 50 patients with spinal cord disease.

2. The responses obtained on double stimulation were mainly extinction and obscuration. Displacement was only rarely observed. Exosomesthesia was not found.

3. Extinction was only rarely present when single stimulation techniques failed to reveal a sensory deficit.

4. When a sensory level was demonstrated through double simultaneous stimulation techniques, it corresponded well with the level of anatomic pathology as later disclosed by myelography or operation.

5. Double simultaneous stimulation phenomena were most frequently elicited when the face was one of the two areas simultaneously stimulated.

6. Double simultaneous stimulation techniques can be used in the examination of psychotic or uncooperative patients and yield valid data.

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The treatment of encephalitis embraces, blood-letting, general and local, purgatives, antimonials, mercurials, cold lotions applied to the head, counter-irritation, &c.

The efficacy and safety of blood-letting depend upon its prompt and effectual administration. I believe the *only* satisfactory mode of the institution of this important remedy is that which I have pointed out in my work on Blood-letting. The patient is to be placed perfectly upright, looking upwards, and bled from a good orifice to *incipient syncope*. In this manner alone can we adapt the remedy to the nature and violence of the disease, and the strength of the patient. To *prescribe* a certain quantity of blood to be taken, is a dangerous, indolent, and unjustifiable proceeding,—for it is impossible to know, a priori, what that quantity should be.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

The Hematologic, Gastric Acidity and Cerebrospinal Fluid Findings in Multiple Sclerosis

A. S. Dekaban, M.D., R. J. Brodrick, M.D. and T. R. Waugh, M.D.

THE laboratory findings in 80 unselected cases of multiple sclerosis, assembled from the records of the Montreal Neurological Institute, have been analyzed for the blood picture, cerebrospinal fluid findings and gastric acidity. Clinical data are briefly discussed to afford a better insight into the severity of the disease and the distribution of the pathologic process in the nervous system.

REVIEW OF THE LIERATURE

Blood findings. Little attention has been paid to detailed blood studies in multiple sclerosis. In 1930 McKenna reported 109 cases of multiple sclerosis, of whom 23 per cent had a leukocytosis varying between 11,000 and 18,000 per cu. mm.[1] and 59 per cent showed either leukocytosis or fever, or both. He concluded that every case of multiple sclerosis may at some time or other show febrile changes and leukocytosis, but he pointed out that these features could not be expected to serve as diagnostic criteria.

Bonadurer (1933), in a study of sedimentation rate in 31 cases of multiple sclerosis,[2] was unable to make any correlation between these values and the clinical picture. The sedimentation velocity was normal in 21 cases, increased in ten. In five of the latter, however, it was not certain that some other cause was not responsible for this rise.

Simon and Solomon (1935) noted a prolonged decrease in coagulation time in 12 cases of multiple sclerosis following the intravenous injection of typhoid vaccine or the subcutaneous injection of epinephrine.[3] This was greater than that found in 14 controls. They suggested that the coagulation defect caused an increased tendency towards intravascular clotting. In 1942, Simon repeated the studies, this time including other diseases of the brain stem and spinal cord.[4] He showed that all cases responded to typhoid vaccine and to epinephrine with a decrease in coagulation time. The drop was more striking in multiple sclerosis than in the other diseases.

From the Montreal Neurological Institute, the department of neurology and neurosurgery, and the department of pathology, division of hematology, McGill University, Montreal, Canada.

Putnam (1936) noted no marked variation in prothrombin time, but observed an unusually large number of multiple sclerosis patients with high fibrinogen values.[5]

Reese, in 1944, stated that in 241 cases studied, total and differential blood counts could not serve as diagnostic criteria for exacerbations and remissions of multiple sclerosis.[6] He evaluated coagulation time in 28 cases of intermittent multiple sclerosis; in all but one instance this was normal. In 20 of these cases, however, an abnormality in prothrombin time was found, indicating an apparent hypoprothrombinemia.

This review suggests that while there are no typical hematologic findings in multiple sclerosis, certain changes not infrequently exist.

Gastric acidity. There are not many reports of studies of gastric acidity in multiple sclerosis. In 1933, Haug found among 22 patients with this disease, ten with hyperacidity, seven with normal acidity, and five with sub-acidity.[7] Dattner (1937) reported 90 cases, of whom 37 per cent had anacidity.[8] Lesny and Polacek (1948) found that among 88 patients, 23 (26 per cent) showed achlorhydria.[9]

Vanzant et al. (132) studied records of 3,746 patients without obvious gastrointestinal disease.[10] The incidence of gastric achlorhydria was found to increase with age. Between the ages of 25 and 29 it was found in 3.6 per cent of males and 5.8 per cent of females; between the ages of 40 and 44, the percentage was 10.3 for males and 10.9 for females; between the ages of 50 and 54, it was 18.5 for males and 15.8 for females. It was not mentioned in any of the reports whether histamine injection had been used.

The review of the literature shows that there is no significant increase of the incidence of achlorhydria in multiple sclerosis patients over normals.

Cerebrospinal fluid. Freedman and Merritt summarized the findings in 2,881 cases of multiple sclerosis from the literature up to 1950, including their own 250 cases.[11] They found an increase in cell count above 5 cells per cu.mm. in 35 per cent of the cases, elevated protein in 33 per cent, and "positive" colloidal gold reaction in 58 per cent of all cases. Previous authors had differentiated types of curves in 2,035 of these cases, and first zone colloidal reaction was found in 24 per cent. Freedman and Merritt concluded that there was no clear evidence of parallelism of either elevated proteins or abnormal colloidal reactions to the clinical course of the disease. However, cell count elevation seemed to them characteristic of an exacerbation of multiple sclerosis.

CASE MATERIAL AND CLINICAL DATA

For the purposes of this analysis, the 80 cases were divided into three main groups:

A. Classical form with remissions and exacerbations—43 cases (54 per cent).
B. Progressive form without remissions—31 cases (39 per cent).
C. Cases studied during onset of disease, i. e., within first six weeks—6 cases (7 per cent).

A further breakdown of these groups is given in table 1.

TABLE 1

MULTIPLE SCLEROSIS

Stage of the Disease	Number of Cases	Form of the Disease	Location of pathological process according to signs of involvement of central nervous system	Number of Cases
Mild	28	Classical form with remissions and exacerbations) 43 cases	1—Spinal cord involved only	8
			2—Brain involved only	4
			3—Optic nerves involved only	–
Advanced	11		1 and 2	14
			1 and 3	8
Severe	4		2 and 3	1
			1 and 2 and 3	8
Mild	17	Steady Progressive Form 31 cases	1—Spinal cord involved only	13
			2—Brain involved only	1
			3—Optic nerves involved only	–
Advanced	8		1 and 2	7
			1 and 3	4
Severe	6		2 and 3	–
			1 and 2 and 3	6
Mild	4	Onset of Disease 6 cases	1—Spinal cord involved only	1
			2—Brain involved only	1
			3—Optic nerves involved only	–
Advanced	–		1 and 2	3
			1 and 3	1
Severe	2		2 and 3	–
			1 and 2 and 3	–

Mild form—Patient able to work full time.
Advanced form—Patient able to look after himself but not able to carry on full time work.
Severe form—Patient not able to look after himself; frequently bedridden.

Four of the 80 patients had mild genitourinary infection. Out of 80 patients, 12 were in the severe state of the disease, 19 advanced and 43 mild.

From clinical evidence the pathologic process was found to involve the spinal cord alone in 22 out of 80 patients; brain alone in six; brain and spinal cord in 27. Involvement of spinal cord and optic nerves together was present in 13 patients. Serological tests for syphilis were negative in all, and there were no severe complicating diseases. Only one patient of the series showed elevation of temperature while in hospital, and this ranged from 100 to 101° for three days. He did not have any obvious infection.

The onset of the disease occurred in five patients before the age of 20, in 31 between the ages of 20 and 30, in 32 patients between the ages of 30 and 40, and in 12 patients over 40 years of age. The majority (79 per cent), therefore, developed the first symptoms and signs of multiple sclerosis between 20 and 40 years of age, which is in accordance with the findings of most other investigators.[12] In this series women prevailed over men in a ratio of 52 to 28.

HEMATOLOGIC FINDINGS

In each of these cases a complete morphologic blood examination was carried out in the hematologic laboratories of the department of pathology of McGill University. This included the sedimentation rate, various tests for

bleeding, coagulation and capillary fragility, and quantitative van den Bergh reactions. The same technical methods were used in all instances. Any hemoglobin level below 90 per cent in a male and 85 per cent in a female was considered abnormal.

Of the 43 cases in group A (with remissions), 18 (42 per cent) showed some degree of anemia. However, only two cases, both females, had hemoglobin levels less than 80 per cent, the lowest being 67 per cent. In 13 cases the anemia was normocytic normochromic in type, and in five it was hypochromic normocytic.

Of the 31 cases in group B (progressive form), 13 (42 per cent) showed decrease in hemoglobin. Four cases had hemoglobins under 80 per cent—two males and two females. The lowest level was 56 per cent. Nine cases were normochromic normocytic anemias, while four were hypochromic normocytic.

Of the six cases in group C (onset of the illness), one showed a very slight hypochromic normocytic anemia. This was a female with a hemoglobin level of 84 per cent.

Thirty-two cases (40 per cent) showed some degree of anemia. However, only six cases had hemoglobin levels under 80 per cent. In only one case did the reticulocyte count rise above 1.0 per cent.

Erythrocyte fragility was determined by the method described by Waugh and Asherman.[13] In no case was hemolysis abnormal.

Sedimentation rate was determined by the method of Wintrobe. All readings were corrected to a packed cell volume of 47.5 per cent irrespective of sex, and any reading over 10 was considered as elevated. In group A, 23 cases (54 per cent) showed acceleration; 19 had 10 to 20 mm., and four had over 20 mm. In group B, 18 cases (58 per cent) had increased rates 13 had 10 to 20 mm. and five had over 20 mm. In group C, three cases (50 per cent) showed elevated erythrocyte sedimentation rates, only one case exceeding 20 mm. Of the 80 cases, therefore, 44 (55 per cent) showed some increase in the sedimentation velocity.

White blood cells. The normal white cell range is considered to be between 5,000 and 7,500 per cu.mm. and any figure over 7,500 is considered abnormal. In group A, 21 cases (49 per cent) showed a leukocyte value above 7,500 per cu.mm. Only seven, however, had counts above 9,000. In group B, 14 cases (45 per cent) had elevated white cell counts, but only three had totals over 9,000. In group C, three cases (50 per cent) showed elevated counts, only one of these having a value above 9,000. The highest figure encountered in the entire series was 13,800 per cu.mm.

Therefore, some degree of leukocytosis was found in 38 cases (47 per cent), although only 11 of these had counts over 9,000. Leukocytosis was nearly always due to a neutrophilia. There was an overall incidence of neutrophilia (over 5,000 neutrophiles per cu.mm.) in 39 cases (49 per cent). Only two patients had eosinophile counts above 400 per cu.mm. (upper limit of normal). Monocytosis (over 550 per cu.mm.) was present in 14 cases but

in all of these it was only slight.

Platelets and coagulation factors. In all groups the majority of platelet counts fell within the normal range of 150,000 to 250,000 per cu.mm. In no case was there a thrombocytopenia. Bleeding time was prolonged in only one instance. There were no abnormalities of fibrin formation or coagulation. In only two cases a slight prolongation of prothrombin time was noted. The Rumpel-Leede test was negative in all patients.

Serum bilirubin. Hyperbilirubinemia was encountered in two cases. Both were in group A, and figures of 1.92 mg. per cent and 1.38 mg. per cent were obtained. In each of the two cases a Takata-Ara test was negative.

GASTRIC ACIDITY

Forty-six patients were examined. Those who did not have free hydrochloric acid were injected subcutaneously with 0.5 mg. of histamine.

Thirty-nine patients (85 per cent) had normal findings (free hydrochloric acid ranging from 15 to 20, and combined acidity from 35 to 65). In the remaining seven patients achlorhydria was found. These results do not differ from the normal.

CEREBROSPINAL FLUID

All samples were clear. Cell counts were carried out within four hours. Total protein was determined by the photoelectric method described by Cipriani and Brophy.[14] Colloidal gold reaction was estimated by the Lange method as outlined by Kolmer and Boerner.[15]

Strong first zone reactions were considered to be those having at least three 5's in the first half of the series; weak first zone, those having at least one 5. A curve was classified as normal or flat if there were no figures above 2. There were no strong mid-zone or end-zone curves.

Total protein below 45 mg. per cent and cell count below six per cu.mm. were considered normal. Of 78 fluids examined, 29 (37 per cent) showed no abnormality; the remaining 49 (63 per cent) showed one or more kinds of abnormality.

Elevation of total protein was found in 27 instances (35 per cent). In only one was this higher than 90 mg. per cent; in other cases it ranged between 45 and 90 mg. per cent. Among 20 patients in the acute stage of the disease (onset or exacerbation), six had elevation of total protein; among 57 patients who were not in the acute stage, 21 had elevation of protein. These figures show that there is no relationship between acuteness of the disease and elevation of total protein, agreeing with findings of Freedman and Merritt.[11]

Elevated cell counts were found in 10 (13 per cent) of 78 samples examined. Among 20 patients who were in the acute stage, two had elevated cell counts; among 58 patients who were not in the acute stage, eight showed elevation of the cell count. Freedman and Merritt's findings, that patients in the acute stage show a higher incidence of elevated cell count than chronic cases, is not corroborated by our findings.[11]

First zone colloidal reaction (71 fluids examined) was found in 28 in-

stances, or 40 per cent; strong first zone reaction was present in 17 and weak first zone in 11 cases.

SUMMARY

Eighty cases of multiple sclerosis have been studied. The results of morphologic blood studies, coagulograms and tests of gastric acidity and cerebrospinal fluid examinations are reported.

There was no constant hematologic pattern. Minor abnormalities which occurred could not be correlated with the clinical features of the disease. Slight anemia was present in 32 patients (40 per cent), although only six had hemoglobin levels below 80 per cent. Red blood cells were normal with the exception of a few instances of moderate anisocytosis.

Moderate leukocytosis was found in 38 cases (47 per cent). This was usually due to neutrophilia.

Platelet counts, bleeding time, clotting time, Rumpel-Leede test and serum bilirubin were usually within normal limits.

The sedimentation velocity of red blood cells was accelerated in 44 instances (55 per cent), however, the increase was slight.

The incidence of achlorhydria in our patients was no higher than normal.

Examination of the cerebrospinal fluid in patients suspected of multiple sclerosis is useful, since 64 per cent show some kind of abnormality. In the differential diagnosis between hysteria and multiple sclerosis, positive findings in the cerebrospinal fluid, especially a first zone colloidal gold reaction, may be helpful.

No correlation between acuteness or exacerbation of the disease and elevation of total proteins, cell count, or presence of a first zone colloidal reaction in the cerebrospinal fluid could be found.

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Trauma in Multiple Sclerosis

David J. Flicker, M.D.

Over a period of years numerous factors in multiple sclerosis have been clarified. In statistical studies it has been shown that there is a marked stability in the incidence and death rate from multiple sclerosis, with no difference in regard to sex. Further, it has been shown that the incidence in the white race is far greater than that in the non-whites, that it is more frequently noted in northern or cold climates as compared to southern or warm climates, that there are no urban-rural differences, that there are no occupational relationships which are constant, and that the greatest number of cases have their onset between age 15 and age 40, with the peak probably about 28. Factors such as these are, for the most part, accepted without argument. Yet the implications of these data often seem to be overlooked in the discussions of etiology, particularly in its relationship to the factor of trauma.

One of the conclusions arrived at by the Association for Research in Nervous and Mental Diseases in 1921 was, "In a small percentage of cases it (multiple sclerosis) appears to be excited by trauma, but trauma itself cannot cause it, but it may awaken a disease process already potentially existent."[1]

The superior court of the state of New Jersey has recently rendered a decision on the three following cases of multiple sclerosis:

Case 1.—A 22 year old secretary, sitting at her stenographer's swivel chair, pushed the chair back and fell to the floor on her back or buttocks toward the left side. Following the accident, she complained of pain which she said became progressively worse. She continued her employment, but stated she was unable to perform the same duties because of severe headache, failing sight, and backache with pain running down the back of her legs to her ankles affecting the left side more than the right. After several months she became so incapacitated that it was necessary for her to give up her employment. The court decided, "On the basis of the evidence we conclude that the accident suffered by the petitioner materially aggravated and accelerated the progress of her pre-existing disease (multiple sclerosis) and thereby produced the disability suffered by her." [2]

Case 2.—A man suffered a back strain while he and another man were lifting a piece of iron weighing two to three hundred pounds. Six months later he was diagnosed by a

From the department of neurology, New York University College of Medicine, New York City.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1952.

neurologist as having multiple sclerosis. There is no evidence of symptoms that can be associated with multiple sclerosis prior to five months after the injury. The court decided, "It is possible indeed that the back injury and the appearance of a disease of the spinal cord a few months later were entirely independent of each other, but it is unlikely. On the whole, we are persuaded by the proofs that appellant's disability was caused by the accident." [3]

Case 3.—Subsequent to an injury in February involving his back, a man was adjudged in December as having suffered 25 per cent of disability. Three years later, on a reopening of this case, the disability was increased to 40 per cent. The following year, on an appeal for total permanent disability, the case was brought to the superior court. The court held that, "On February 21, 1943, the petitioner was struck on the back . . . . and as a result thereof developed a condition known as multiple sclerosis." [4]

It should be remembered that every decision regarding medical conditions made by referees and upheld by the courts is based upon medical testimony of some physician or physicians, and we should bear this in mind when offering criticisms of these decisions.

One can find data to support any belief in the literature. Wilson[5] stated, "What part previous trauma may enact in the evolution of this disease is a quaestio-vexata." He continued, " . . . . war experience has provided me with only a few cases where connection between injury and multiple sclerosis has to be considered . . . ." The scarcity of multiple sclerosis amid the welter of war naturally strengthens disinclination to attach importance to injury in civilian life . . . . Now and again the sequence of events does not allow accident to be lightly dismissed." He presented a case in detail and refuted the causal relationship of trauma immediately thereafter by stating, "That patches of spinal sclerosis can be caused by a blow on the forearm is an untenable proposition . . . . It is therefore unwise to disallow the possible influence of external causes and best to adopt a noncommittal attitude, judging every case on its merits."

We thus have a situation where the more recent, accepted standard textbooks on neurology can be quoted either for or against the theory of a possible relationship between trauma and multiple sclerosis.

Some of the conflicting material by authorities on the subject of multiple sclerosis is herewith presented. Brickner[6] stated conservatively that, "Trauma and surgery give the appearance of being less potent as precipitators than might be expected." Shortly thereafter he said, "Laminectomy seems to do no harm in multiple sclerosis, a fact brought out many years ago by Charles Elsberg." But in the same article, he felt that possibly allergy, pregnancy, chilling, lumbar puncture, emotional disturbances, fatigue, and nutritional inadequacy were all factors to be considered in the aggravation of multiple sclerosis. There would seem to be a marked contradiction in his feeling that lumbar puncture can cause an exacerbation of multiple sclerosis and his apparent acceptance of Elsberg's statement that laminectomy can do no harm.

Kolb and associates[7] reported that, "The group that underwent surgical intervention during the disease suggests that patients with multiple sclerosis do not tolerate operations well," providing an interesting contradiction.

Mendel,[8] who is the author most often quoted by the advocates of a relationship between multiple sclerosis and trauma, laid down the following necessary conditions: 1.) direct injury to the skull or spine or violent shaking of the same; 2.) exclusion of other causes of neural illness; 3.) demonstration of complete health before the trauma; 4.) demonstration of a definite temporal connection between the appearance of the first symptoms of the disease and the accident. There is a further implication found throughout the literature that there should be a fairly continuous bridge of symptoms between the injury and the time of the onset of the clinical picture of multiple sclerosis. However, one can find case after case reported in the literature as secondary to trauma where virtually none of Mendel's conditions have been fulfilled. Leube,[9] who published the first case of multiple sclerosis following trauma, stated simply that the injured patient traced his disability to the trauma. It is noted that despite the astonishing number of multiple sclerosis cases reported in the literature, there is not one where trauma can be proved beyond doubt to be the cause, nor any where trauma can be unequivocally proved to be the exacerbating or exciting factor. There are extremely few cases in all the literature in which multiple sclerosis was diagnosed presumably as a traumatic sequelae in which we have anatomic confirmation of the diagnosis. The fact that a patient was able to work and carry on normal activities, presumably until the moment of the occurrence of trauma, is not necessarily decisive, since the ability to work and the presence of a neurologic disease are certainly not mutually exclusive. It is noteworthy that many of the earlier reported cases of multiple sclerosis that were attributed to trauma followed direct and violent trauma to the central nervous system. Again, there is no record of autopsy findings and one wonders, therefore, if the symptomatology noted was not due to multiple areas of hemorrhage and softening in the cerebrospinal axis rather than to multiple sclerosis. Then, too, one finds in the early literature the indictment of such toxins as carbon monoxide, lead, copper, manganese, etc.[11] Refinements in pathologic technics and further study have shown that these play no role in the etiology of multiple sclerosis.[12]

In a recent article it was pointed out that "exogenous precipitating factors in multiple sclerosis are similar to those that tend to increase the coagulability of the blood, namely, infection, trauma, chilling, and pregnancy." In the same article the author stated, "Infections and injuries, though long considered factors which could initiate or exacerbate the disease, could not be proved to play a specific role in another study of a large group of persons with multiple sclerosis." [13]

Numerous authors have stated or implied that there was an increase of the incidence of multiple sclerosis during war or military service and attempted thereby to draw inferences concerning the effect of trauma and exogenous factors. In a recent communication from the office of the surgeon general of the Army,[14] the statement was made that 800 men were discharged from the service with the diagnosis of multiple sclerosis in the years of 1942 to 1945.

With the now accepted incidence of 4.2 per 100,000,[1] it could have been anticipated that over 1200 cases would have developed in the group involved in the same period of time. We might almost make a negative inference to the effect that multiple sclerosis appeared less likely to develop in military service despite the obvious increase in trauma.

Review of the factors found in the literature to which multiple sclerosis has been attributed include the following: working in a confined space with electric light, sunstroke, allergy, pregnancy, chilling, lumbar puncture, emotional disturbances, fatigue, nutritional inadequacy, incidental infections, biological crises, intoxications, alcohol, overheating, burns, poisons, epilepsy, sexual excesses, anemia, business troubles, nervous tension, ordinary coryza, digestive upset, an occurrence of some acute contagious disease in the family, or anything out of the ordinary in the lives of these patients.

When the exact etiology of any disease is unknown, trauma is always held suspect. Patients with chronic neurologic lesions have always been prone to incriminate trauma, either physical or emotional, as the causative agent. Trauma, however, is common and ubiquitous, and it is indeed difficult to obtain a careful history from any patient with any condition without eliciting some history of antecedent accidents.

Apparently, medical authors are ready to accept the patients' explanations without question. The following modifications of Brain's [15] analysis of the relationship between trauma and multiple sclerosis are suggested:

1. That the association is a coincidence. This can be readily accepted by any thinking observer in many of the cases reported.

2. That traumatic or toxic lesions of the nervous system may be mistaken for disseminated sclerosis.

3. That trauma may induce changes in the neighborhood of pre-existent but hitherto latent plaques of disseminated sclerosis and so lead to the appearance of symptoms. This theory would explain our willingness for the present to accept severe cranial or spinal injury as exacerbating or aggravating.

4. That a patient, after spending some time in bed as a result of trauma, may manifest symptoms because he has lost the power to compensate for a defect.

5. That the trauma itself instead of being the cause, may be the result of pre-existing symptoms of disseminated sclerosis. The disease is often present in latent unrecognized form before the injury, the latter serving to draw attention to it.

6. That the trauma may produce in the body a locus minoris resistentia so that if the syndrome of multiple sclerosis should subsequently develop that particular portion of the body might be the first affected.

SUMMARY

1. The literature regarding the relationship of trauma to multiple sclerosis is equivocal and can be quoted in either direction. However, no evidence is presented by which trauma can be justifiably indicted as etiologic of the dis-

ease. Only with direct injury to the skull or spinal cord can it be suspected of aggravation of the disease.

2. When trauma is listed as a cause of multiple sclerosis, it is a denial of the statistical facts that war and automotive and industrial mishaps have increased the accident rate, and there should therefore be a rising rate of deaths due to multiple sclerosis, instead of the constant rate noted.

3. The lack of occupational relationship and sex differences is also disregarded by adherents of traumatic etiology, for statistics reveal a significantly greater incidence of accidents in certain occupations and in the male sex.

4. The lack of urban-rural difference in incidence, despite the preponderance of trauma in urban life is also evidence against the implication of accidents.

5. The constant greater incidence of multiple sclerosis in the white race and in cold climates would give some implication that trauma is more frequent in white than in other groups, and in the north than in the south—again situations which are contrary to fact.

6. The increased incidence in the age bracket of 15 to 40 years would also discount trauma as a factor; that accidents are more frequent in the young and in the aged is well known.

Trauma, in the rare instances noted above, may possibly cause an exacerbation in multiple sclerosis, but it should be dismissed from further consideration in studies of the etiology of multiple sclerosis.

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Modifications of Signs in Multiple Sclerosis With Tetraethylammonium Chloride

Guy H. Williams, Jr, M.D., L. J. Karnosh, M.D. and Howard J. Tucker, M.D.

ALTHOUGH the etiology of multiple sclerosis remains obscure, recent articles dealing with its treatment have emphasized that some vascular disorder is one disturbing factor. This change may be in the form of venous stasis or some change in vasomotor tone.

The factor of vasospasm in the production of pathologic lesions in the central nervous system is not a matter of speculation. A large number of published reports deal with direct observations of the blood vessels in the central nervous system during sympathetic stimulation or after the injection of various drugs. Most convincing are the observations of Franklin and Brickner[1] who relieved retinal vasospasm and scotomata simultaneously by the use of amyl nitrite or intravenous papaverine. They postulate that lesions of multiple sclerosis result from or are associated with vasospasm, that scotomata in multiple sclerosis patients are the result of vasospastic lesions in the retina and that such disturbances apply with equal validity to any portions of the central nervous system.

Lyons et al[2] demonstrated that tetraethylammonium chloride relieves vasospasm by blocking the autonomic ganglia. This fact, coupled with the assumption that the acute or exacerbative signs and symptoms of multiple sclerosis contain the element of vasospasm, led to a study of the effect of this drug on disseminated sclerosis.[3]

Accordingly, tetraethylammonium chloride was administered to 222 patients manifesting the acute and chronic signs and symptoms of multiple sclerosis. The majority of these patients gave a history of having had exacerbations and remissions of the disease. The technique of administration consists of deep intramuscular injection of amounts varying from 350 to 1800 mg. six times weekly. The immediate outstanding effects of the drug are an orthostatic hypotension and loss of visual accommodation. The patient is advised

From the Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

Read at the second biennial meeting of the American Academy of Neurology, Virginia Beach, Virginia, April 11, 1951.

TABLE 1

I. Total number of cases	222	
II. Average age of cases	34	years (approx.)
Oldest—60 Youngest—16		
III. Average duration of illness	4.5	years (approx.)
A. *Arbitrary* Classification as to length of illness		
(1) Signs and symptoms two months and less—acute	79	
(2) Signs and symptoms over two months—chronic	143	
	222	Total
IV. Group Classification of Treatment Results		
A. Good Subjective and Some Objective Improvement		
B. Fairly Good Subjective and Minimal Objective Improvement		
C. Fair Subjective and No Objective Improvement		
D. No Improvement		

to remain in a supine position for one hour to avoid syncope and excessive dizziness. The effective dosage varies greatly in individual patients. A sensation of mild faintness and giddiness upon arising one hour after administration of the drug has generally been considered to be indicative of sufficient dosage. Once the dose is standardized, starting with a small amount and increasing it gradually to the optimum level, the maintenance dose is given daily six times weekly until the desired effect is achieved or until there is no progress in improvement.

In surveying the patients treated with tetraethylammonium chloride, those in whom the diagnosis was doubtful and in whom less than five injections had been given were discarded. An attempt is made to evaluate the results in 222 cases treated over the past two or three years. Each of the individuals in this series has been worked up thoroughly from the standpoint of neurologic examination and any other clinical studies necessary to eliminate doubtful entities. In general, it might be said that the signs and symptoms of these 222 patients are typical of disseminated sclerosis.

The average age of the group was 34 years, the oldest patient being 60 and the youngest 16. The average duration of illness was approximately 4½ years, although this figure is unreliable since it is difficult in most instances to state accurately the time of onset of the disease (table 1).

In evaluating the results of treatment, an arbitrary division was made at two months' duration of the signs and symptoms. Those having symptoms of two months or less were considered to be acute and those manifesting signs and symptoms for two months or longer were classified as chronic. When a chronic patient had an exacerbation of acute signs and symptoms and treatment was instituted at this time, the results were classified among those in the acute phase. The number of acute cases totalled 79 and those in the chronic phase totalled 143. The smallest number of treatments given to any patient in this series was five.

Considering the kaleidoscopic nature of multiple sclerosis, one is immediately confronted with a most involved problem in the evaluation of the results of any form of treatment. The present situation is further complicated in that a majority of the patient population reside out of the city of Cleveland,

TABLE 2

Group A.	Good Subjective and Some Objective Improvement		
	(1) Acute	12)	
		)	18
	(2) Chronic	6)	
Group B.	Fairly Good Subjective and Minimal Objective Improvement		
	(1) Acute	24)	
		)	50
	(2) Chronic	26)	
Group C.	Fair Subjective and No Objective Improvement		
	(1) Acute	22)	
		)	63
	(2) Chronic	41)	
Group D.	No Improvement		
	(1) Acute	21)	
	a. Worse on Treatment — 4	)	91
	(2) Chronic	70)	
	a. Worse on Treatment — 13		
		222	Total

making follow-up study difficult. An attempt is made to classify the results of tetraethylammonium chloride therapy as follows:

Group A, in which there has been good subjective and some objective improvement. Notable in objective modification has been change in visual fields, alteration in the deep and superficial reflexes, and improvement in coordinated movements.

Group B includes those patients manifesting fairly good subjective improvement and little objective change for the better. Typical of this group have been those showing definite decrease in paresthesias, improvement in vision, modification of the gait, and improvement of bladder control.

In *Group C* are classified those who manifested fair subjective improvement with no objective change for the better. These results are typified by a sense of generalized well being, mild improvement in paresthesias and vision, mild correction of gait and coordinated movements.

Group D consists of those patients showing no improvement.

The results of treatment are shown in table 2. It should be pointed out that under no circumstances is tetraethylammonium chloride considered to be specific in the treatment of multiple sclerosis. Likewise, it is to be remembered that the favorable responses are recorded with a full awareness of the spontaneous remissive factor in multiple sclerosis. No positive argument can be made to show that the benefits can be attributed entirely to this drug. However, in some instances startling changes in signs or symptoms have been observed within a matter of one to two days after the initial administration of tetraethylammonium chloride. One very notable case is that of a young woman, age 20, who presented herself with paraplegia of the lower extremities. There were other accompanying signs in the cranial nerves and upper extremities to substantiate the diagnosis of multiple sclerosis. She experienced mild return of motor power in the lower extremities within one to two hours after the first administration of tetraethylammonium chloride, whereas prior to that she had been unable to move the legs for at least several weeks. Other patients have remarked that paresthesias were less intense, or that visual disturbances showed improvement, or that even muscular coordination in the hands improved after two or three injections.

A number of instances have been noted in which exacerbations occurred following the cessation of tetraethylammonium chloride therapy. In a few such instances, tetraethylammonium chloride failed to give relief in the period of exacerbation.

In the entire series only two patients were encountered who were unable to tolerate tetraethylammonium chloride, due to undesirable side effects. No complications were noted except for occasional attacks of rather severe dizziness, rare bouts of nausea and soreness of the muscles of the buttocks.

At most, tetraethylammonium chloride appears to be only a palliative treatment, particularly helpful in the acute phase of the disease. Only moderate to no improvement can be hoped for in the chronic stage. Providing tetraethylammonium chloride is given in the early phase of an exacerbation of multiple sclerosis, it is possible that it may prevent the formation of new "scars" in the central nervous system.

While these data are not greatly optimistic regarding the future of tetraethylammonium chloride in multiple sclerosis, this drug may be of value in selected patients. This study can only be considered as a stepping stone toward some understanding and modification of the disease process.

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It has been asserted, from similar facts, that the anterior lobes of the brain govern the speech; the corpora striata, the inferior extremities; and the thalami, the superior extremities; but I fear these deductions are not sufficiently substantiated. The same remark must be made relative to the supposed connection between the cortical portion of the cerebrum and the intellectual faculties, and the cineritious portion, and the movements.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

Treatment Review

Stellate Block

Technique, Dangers and Safeguards

William V. Trowbridge, M.D., Allan E. Bayless, M.D. and John D. French, M.D.

STELLATE BLOCK has been recommended in the treatment of a diverse group of diseases. Among the clinical conditions in which this procedure has found enthusiastic use are Raynaud's disease, traumatic acute arteriospasm of the upper limb, causalgia, acrocyanosis, hyperhidrosis and amputation neuromata.[1] Ochsner and DeBakey[2] have urged its use in the management of thrombophlebitis of the upper limb, and Bageant[3] has reported good results in the treatment of pulmonary embolism. Interruption of the cervical sympathetic chain by this method has been recommended also in the treatment of angina pectoris, bronchial asthma[4] and postencephalitic parkinsonism.[5] Karnosh[6] has reported improvement in thalamic pain and in psychoses with states of depression, following stellate block, and Dworacek[7] feels that the procedure has benefitted his cases of Ménière's disease, chronic otitis media, otosclerosis, tinnitus and ozena. Anesthetization of the superior cervical ganglion, in a manner similar to that used for the stellate ganglion, has even been employed to hasten the healing of fractures in all extremities.[8]

Stemming from the first reports by Leriche and Fontaine in 1936,[9] this procedure has found recent broad acceptance in the management of cerebrovascular accidents. Since the cerebral vessels receive sympathetic innervation in large part from the carotid plexus, it is felt that interruption of impulses through this pathway relieves the widespread, irritative vasospasm which surrounds the site of vascular insult.[10] In this manner, the ischemic area would again be nourished, and nervous elements which had not been irreversibly damaged would again function. Conflicting experimental data have been presented to support or refute this theory, but the preponderance of evidence appears to favor the therapeutic use of stellate block.[10–16] In addition, numerous reliable clinicians have reported well-controlled series of cases showing beneficial results following stellate block in the treatment of cerebral thrombosis and embolism.[5, 17–20]

Regardless of reports denouncing the use of this procedure, it has found ready acceptance as a replacement for the "skillful neglect" regimen previously em-

From the neurological surgery section, Veterans Administration Hospital, Long Beach, California.

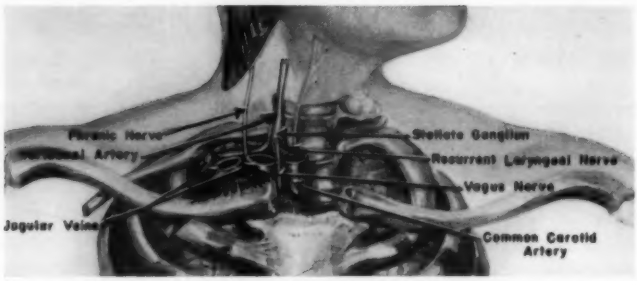

FIG. 1. Illustration of the important anatomic structures in the region of the stellate ganglion.

ployed in the management of these disheartening conditions.

With the professional enthusiasm attending the use of stellate block, there have followed in the lay press, glowing reports of its results. With this knowledge, the patient's family frequently urges the physician to effect such treatment, and on occasion, the institution of such measures has been attempted by those unfamiliar with the technique and unaware of the dangers attending the procedure. The latter are not to be minimized. Indeed, complications arising from stellate block may at times present a problem more serious than the effects of a mild cerebrovascular insult.

A simple technique is presented for anesthetizing the stellate ganglion, emphasizing that the method (with the exception of minor modifications) is essentially that used routinely in various institutions.[17,20,22] Dangers attending stellate block and the measures by which they can be avoided will also be reviewed.

ANATOMIC CONSIDERATIONS

The stellate ganglion, averaging 2 by 2 by 0.5 cm. in size, lies between the transverse process of the seventh cervical vertebra and the neck of the first rib (figure 1). The apices of both lungs lie in close relationship to the ganglion, particularly on the right side where the dome of the pleura rises approximately 1.5 to 2 cm. higher than on the left. The vertebral artery, particularly its first portion, may lie anteromesial or posteromesial to the ganglion,[23,24] and is relatively immovable at this level due to its regional fixation in the cervical vertebrae. Immediately anteriorly there is a

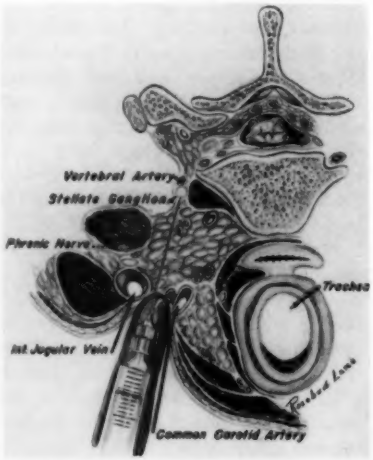

FIG. 2. Schematic body cross-section at the level of C-7 showing the relationship of the stellate ganglion to the cervical nerves and of the hypodermic needle to regional structures during stellate block (after Truex and Kellner).

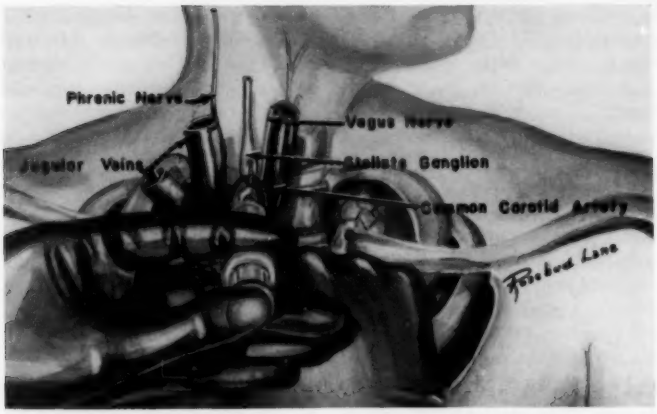

FIG. 3. Technique of stellate block, showing the relationship of the hypodermic needle to regional structures.

close relationship to the subclavian artery, the common carotid artery and the jugular veins. The cervical nerves, as they pass from the vertebral foramina, course near the ganglion. The recurrent laryngeal and phrenic nerves—though somewhat more distant—are separated from the ganglion in large part by areolar tissue only (figure 2). Damage to any of these structures during the mechanical introduction of a local anesthetic agent may produce serious consequences. Simple precautions will minimize damage to regional structures.

TECHNIQUE OF STELLATE BLOCK

1. The head is turned to the side opposite to the ganglion to be blocked, placing the homolateral sternomastoid muscle under mild tension (figure 3).

2. A previously prepared syringe, containing 5 ml. of a suitable aqueous anesthetic solution (2 per cent Procaine or Novocaine) is attached to a 2-inch, 20 gauge hypodermic needle.

3. The area centering about the sternal attachment of the sternomastoid muscle is cleansed with a suitable topical antiseptic or detergent.

4. With a sterile glove, the index finger of one hand is pressed firmly in a posterior direction in the small notch between the sternal and clavicular heads of the sternomastoid muscle. The transverse process of the seventh cervical vertebra frequently may be palpated as a landmark by the compressing index finger.

5. While maintaining the firm posterior pressure, the syringe is taken in the other hand and the needle introduced just cephalad to the compressing finger.

6. The needle is directed perpendicularly to the long axis of the spine, angled mesially about 5 degrees from the vertical, and is then passed dorsally in a straight path until bone is encountered.

7. Upon striking bone, the needle is withdrawn 2 to 3 mm., and the pressure of the opposite finger is relaxed.

8. Careful aspiration is effected, and if air, blood or cerebrospinal fluid is obtained, the needle is withdrawn and the procedure repeated with the needle in a slightly altered plane.

9. Should aspiration be negative, the contents of the syringe are slowly injected.

10. A homolateral Horner's syndrome should appear within five minutes.

Elaborate preparation of the skin with superfluous draping of the site of injection is as unnecessary as for any other medicinal injection. Moreover, elaborate preparation of the area frequently leads the conscious patient to feel that an extensive procedure is under way,

with a resultant predisposition toward poor cooperation. The posterior pressure with the index finger tends to deviate large vessels from the line of puncture (figure 2), and veins which are not so deviated are flattened, thus clean punctures are made. The needle introduced in this plane forms an angle of about 60 degrees with the long axis of the cervical neural foramen, minimizing the possibility of subarachnoid injection. Following contact with bone, the needle is withdrawn slightly to prevent subperiosteal injection of the fluid and to place the tip of the needle in the paravertebral areolar tissue, where wide diffusion of the anesthetic will take place. By this technique, bone is usually encountered by the needle within 2 to 3 cm. from the surface of the skin. This is in contrast to the depth of puncture necessary in other methods, wherein a block of tissue measuring 5 to 7 cm. is ordinarily traversed.[25]

Horner's syndrome obtained by this procedure will seldom be complete. Miosis and a visible increase in conjunctival vascularity are the most constant effects. Ptosis and enophthalmos, although usually present, may be minimal or absent.

DANGERS

The dangers inherent in any procedure in which blind attempts are made to approach the stellate ganglion hinge upon the proximity of numerous vital structures to the ganglion. These are listed as follows:

Extravasation of blood from a damaged vessel is seldom of clinical significance, in that it is usually limited to a small regional hematoma. It must be remembered, however, that large vascular tears can be produced by indiscriminate "churning" motions with the needle. It is entirely possible that a sufficiently large collection of blood might follow large venous tears to produce jugular compression. Ordinarily this would be insufficient to effect notable damage, but in those cerebrovascular accidents with markedly elevated intracranial pressure this added obstruction to the venous drainage of the brain may prove disastrous. Direct approach toward a given desired point with the needle will minimize such extravasation, since clean punctures of blood vessels tend to close spontaneously. A death has been reported after percutaneous carotid angiography,[26] following extravasation from the same large vessels that are endangered in stellate block. Procedures involving complicated, geometric manipulations of the needle in approaching the ganglion should be avoided.

Intravascular injection of a local anesthetic agent into the carotid, vertebral or subclavian arteries can produce serious results. Such injection deposits the anesthetic in a position for distribution to the brain, and in the vertebral artery it would be distributed to the medullary centers producing immediate respiratory collapse.

Case 1.—A 58 year old white man was admitted to the hospital with a profound right hemipelgia and global aphasia. These were rather slow in onset suggesting, with other elements of the history and physical findings, a cerebral thrombosis. On the day of admission a left stellate block was performed. During injection of the local anesthetic the patient developed pronounced nystagmus and vomited; following this, he precipitously stopped breathing. Artifical respiration was instituted immediately and after about 5 minutes the patient began to breathe spontaneously.

Prevention of such an accident may be effected simply by careful aspiration with the syringe prior to injection. Should blood be aspirated, the needle should be withdrawn and again inserted, rather than manipulated while it lies deep in the tissues. On rare occasions the tip of the needle may lie in an artery in such

fashion that aspiration will produce no blood. Should injection result in respiratory arrest, with or without antecedent nausea, vertigo or nystagmus, artificial respiration until the effects of the drug have been dissipated will usually prevent death.

Subarachnoid injection of anesthetic agents while attempting stellate block may occur, particularly if the angle of approach parallels the long axis of the cervical neural foramen. The deleterious effects of such an injection need no description, and two deaths have been referred to in the literature following such an accident[18]. Injection need not be made directly into the subarachnoid space, since it has been shown that fluids forcibly injected beneath the perineurium may dissect proximally to enter the cerebrospinal fluid[27]. Aspiration with the syringe may not reveal that the needle is in the subarachnoid space, since negative pressure at the tip of the needle frequently draws delicate membranes to it, occluding the opening. It has also been noted that introduction of the needle into the cervical foramina and the subarachnoid space, even with forcible aspiration, may be unattended by pain.[28] Introduction of the needle as nearly perpendicular as possible to the cervical neural foramen is the obvious method of approach to avoid entering it. Should radiating pain appear in the shoulder or arm during the procedure, it is probable that a nerve trunk has been encountered and the needle should be withdrawn to be redirected in a new plane.

Laceration of the pleura with the needle and associated pneumothorax is a rather commonly reported complication of stellate block[1, 3, 4, 25, 28]. Since the dome of the pleura projects to a level above the stellate ganglion, particularly on the right side, the direction of approach becomes of great importance. Lateral, angled anterolateral, and posterior approaches are all potentially dangerous in this respect. Should air be obtained upon aspiration with the syringe it is almost certain that the lung has been penetrated. In such an event, the needle should be withdrawn and re-inserted. Any attempt to redirect the needle while deep in the cervical tissues can produce large tears in the visceral pleura, and such manipulations should be strictly avoided. A small needle puncture of the lung is ordinarily insufficient to produce a pneumothorax of any clinical significance.

In a patient with a cerebrovascular accident it is a common tendency to suspect any respiratory difficulties to be of central origin. Should respiratory distress appear following stellate block, every effort should be made to assure oneself that a pneumothorax is not the cause. Serious difficulties can arise not only from unrecognized pneumothoraces, but from those which have been detected and actively treated.[1, 4]

Case 2.—A 55 year old white man was admitted to the hospital with a flaccid right hemiplegia and global aphasia which began during sleep. He was treated with repeated stellate blocks, and appeared to improve on this regimen. Following one injection he began to breathe heavily and rapidly and then failed to respond. Physical examination revealed hyperresonance of the thorax, and a chest film showed a pneumothorax. At this time the patient showed neurologic evidence of a massive upper motor neuron lesion on the left, as well as the pre-existing right hemiplegia. In spite of active treatment of the pneumothorax, he expired 42 hours later without regaining consciousness. It is postulated that the pneumothorax precipitated cardiac embarrassment which, in turn, was responsible for further cerebral thrombosis.

Anesthetization of nervous structures other than the stellate ganglion may happen easily during stellate block. The rather wide diffusion of local anesthetics in aqueous media through the planes of

areolar tissue in the neck may anesthetize the phrenic or recurrent laryngeal nerves (figure 2).

Case 3.—A 58 year old paraplegic man had suffered repeated myocardial infarctions, with intractable pain in the left shoulder following recovery. Multiple stellate blocks relieved this pain quite well. Approximately 5 minutes following one of these blocks the patient became very hoarse and within another 5 minutes he was completely aphonic. The aphonia persisted for about one hour, following which his voice gradually returned. There was no respiratory embarrassment.

Temporary unilateral interruption of these nerves is seldom attended by notable distress. It is apparent, however, that temporary interruption of both the phrenic nerves or both recurrent nerves would percipitate pronounced respiratory distress. This is of particular note in a class of patients where respiratory difficulties of central origin are quite common. For this, if for no other reason, bilateral stellate block should not be attempted.

The cardiac nerves arising from the cervical sympathetic chain may be stimulated as a result of mechanical irritation by the needle, with attendant anginal pain.[5] In such an event, following quick aspiration with negative results, the anesthetic agent should be injected to terminate the pain. In this instance, it is felt that failure to inject would probably be dangerous.

Anesthetics in an oil vehicle have been employed as a blocking agent to produce prolonged effects and to minimize the frequency of injection.[20] Bearing in mind that any method for blocking the stellate ganglion depends upon a blind approach to an extremely small structure, the necessity for a highly diffusible substance is obvious. Attempts to inject oily anesthetics through a needle left in place, following successful block with aqueous media, frequently fails to produce a prolonged Horner's syndrome. In addition, while intravascular injection of an aqueous anesthetic is quite dangerous, the similar injection in an oil base is even more so. Moreover, slowly absorbed oils injected into the cervical tissue constitute a foreign body and may, if slightly contaminated during the procedure, serve as a nidus for dangerous infection.

Case 4.—While being treated in the hospital for renal colic, which cleared quickly, a 27 year old white man was given a left stellate block for severe causalgia present since a gunshot wound of the left shoulder four years previously. The block, performed with an oil-based local anesthetic, did not produce a Horners syndrome, and immediately after injection the patient developed severe dyspnea and substernal pain. A chest film revealed 60 per cent pneumothorax, with a small amount of pleural effusion. Following this, he developed a severe empyema which required one and a half months of hospitalization for resolution.

Frequent blocks with aqueous solutions are considered to produce more successful interruption of the cervical sympathetic chain than are infrequent blocks with long-acting, oily preparations.

Cerebral hemorrhage is believed to be a contraindication to stellate block by some authors[10, 17], while others have used this procedure in the presence of hemorrhage without obvious deleterious effects.[19] The question is felt to be of only academic importance, but lumbar puncture to determine the presence or abscence of gross blood should precede the initiation of stellate block therapy in all cases. Acute subarachnoid hemorrhage is a definite contraindication to this procedure.

Convulsions following injection of local anesthetics may occur, due to initial stimulation of the central nervous system by these drugs. This is seen rarely, and only in individuals who are sensitive to the drug. The symptoms can be readily controlled with small doses of barbiturates.[20] In conscious patients such seizures

can be obviated largely by the administration of two grains of phenobarbital prior to the procedure. In stuporous or disoriented patients it is probably better to allow the very occasional convulsion rather than depress the central nervous system further with barbiturates.

Extreme sensitivity to local anesthetics is quite rare, although deaths are reported to have occurred following the injection of as little as 0.01 Gm. of procaine.[29] Death occurs immediately after injection and is caused by cardiovascular collapse. Such reactions are probably due to extreme idosyncrasy. Sala de Pablo records an accident of this type in which a patient immediately expired following injection of 25 ml. of 2 per cent Novocaine for brachial plexus block.[30] Autopsy revealed no anatomic explanation for the death.

It is doubtful if such a catastrophe can be averted by routine conjunctival testing for sensitivity. A standard procedure of conjunctival or skin testing with the anesthetic to be employed is commendable, however, and stellate block should probably not be done in the presence of obvious extreme sensitivity.

Cerebrovascular accidents secondary to cerebral neoplasms are known to respond to stellate block in a fashion similar to those due to arterial disease alone. Patients with tremendous neoplasms have been seen to respond to this type of therapy with short-lived functional improvements.

Case 5.—A 72 year old white man had a marked left hemiplegia, relatively slow in onset. Clinical and laboratory examination led to a clinical diagnosis of cerebral thrombosis, involving branches of the right middle cerebral artery. Shortly following admission the patient became comatose and exhibited Cheyne-Stokes respiration. A stellate block was performed, following which he dramatically regained consciousness, sat up in bed, and carried on a normal conversation. During the following two weeks, varying degrees of depression of consciousness were improved by repeated stellate block. One evening, however, the patient suddenly developed generalized convulsions, became deeply comatose, and expired. At no time was there an alteration of the original clinical diagnosis.

Autopsy revealed an infiltrative tumor, involving the entire right frontoparietal region. Microscopically this tumor was shown to be a magnocellular glioblastoma multiforme.

In such a case, the failure to make a correct diagnosis is only productive of academic embarrassment, since the lesion is malignant and there is little therapy that could be attempted. The presence of a vascular lesion, or lesions, secondary to a cerebral neoplasm, is by no means a contraindication to stellate block. It is unfortunate, however, when a favorable response to this therapy is held to confirm a diagnosis of a vascular lesion secondary to arterial disease alone. Such an instance is seen in the following case:

Case 6.—A 63 year old white man was admitted to the hospital with a history of weakness in the right hand and leg and speech disturbances, all developing slowly over the period of a year. At the time of admission he was almost totally aphasic. No papilledema was present. A clinical diagnosis of cerebral thrombosis was made, and he was treated over a period of two months with stellate blocks, which on repeated occasions were followed by improvement in the motor power of his right limbs. Two months after admission he suddenly developed severe convulsions and expired. At autopsy, there was a large 3.5 x 2.5 x 2.5 inch meningioma found parasagitally, severely compressing the left frontal lobe.

Cerebral neoplasms may frequently become manifest only through their precipitation of a regional thrombosis, particularly when the tumor arises in the relatively silent, non-dominant temporal lobe. Clinical improvement of the patient following stellate block therapy should never minimize the efforts of the physician to arrive at an accurate etiologic diagnosis.

SUMMARY

1. The anatomic relationships of the stellate ganglion are reviewed.

2. A simple, relatively safe technique for effecting stellate ganglion block is described.

3. The common complications following stellate block are enumerated, together with precautions to minimize their frequency.

4. Interruption of the cervical sympathetics by stellate block should never serve a diagnostic function in the management of cerebrovascular accidents. A favorable response to this procedure does not eliminate a cerebral neoplasm as the inciting agent in a cerebral thrombosis.

5. The dangers attending the procedure are sufficiently great to discourage its use in the treatment of very mild neurologic deficits, or for those complaints secondary to remote cerebrovascular insults.

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Neurology

Clinical Pathologic Conference

From the Sections of Neurology and Psychiatry,
Mayo Clinic, Rochester, Minnesota

Presented by Joe R. Brown, M.D.‡
and James A. Bastrom, M.D.†

CASE PRESENTATION

A 37 year old married merchant was referred to the Mayo Clinic with the chief complaint of headache. The past medical history was not contributory. Eleven months before admission he noted the insidious onset of occipital headaches. They were described as a dull pressure radiating to the vertex and eyes and usually coming on about noon. The headaches increased in frequency until they occurred daily. Six months before admission he noted blurred vision but an eye examination gave negative results. Four months before admission the visual fields were reported as diminished. At about that time he had two evening chills with a temperature of 102 degrees F. The headaches were of increased intensity and were associated with nausea and vomiting. The results of physical and neurologic examination, urinalysis, blood culture, and roentgenographic examination of the head were negative and the blood counts were normal. The patient began regularly to have an elevation of temperature up to 99.6 degrees F. The spinal fluid was under normal pressure, the cells numbered 500 per cu. mm. of which 50 per cent were polymorphonuclear leukocytes, and the protein content was 300 mg. per 100 ml. The gold curve was said to be "as seen in infection" and the Kline reaction was negative. Guinea pig inoculation gave negative results. At this point, about three months before admission, he was hospitalized for six weeks. He received a trial of treatment with a succession of antibiotics, a sulfonamide, typhoid vaccine, and Corticotropin (ACTH), the last-named drug being given for ten days. Personality change, depression and "symptoms like those of diabetes insipidus" appeared. Intramuscular injections of vasopressin (Pitressin) controlled the last-mentioned group of symptoms. A

Case presented at a combined meeting of the section of neurology and the section of Pathologic Anatomy, Mayo Clinic. Throughout this paper a dagger (†) indicates a fellow of the Mayo Foundation, a double dagger (‡) a consultant of the Mayo Clinic.

trial of treatment with cortisone failed to produce a response; however, it was said that the personality change was reversed and that the patient became afebrile after a trial of treatment with Corticotropin and Streptomycin. After discharge from the hospital, the patient relapsed, with increased headache, fever, depression, restlessness and somnolence. A second four-week course of treatment with Corticotropin and Streptomycin resulted in improvement except for the patient's eyesight. A third relapse, two weeks before admission, failed to respond to treatment with Corticotropin and Streptomycin, and the patient was referred here for further care.

DR. BASTRON: Dr. Frazier, would you start out by commenting on this man's history?

DR. S. H. FRAZIER†: Significant points in the history of this 37 year old patient are the headache of 11 months' duration; the visual blurring of six months' duration; the development, five months ago, of intermittent fever, personality change, depression and symptoms like those of diabetes insipidus; the increased cell count and protein content of the spinal fluid; and his response to treatment at various times with antibiotics, Corticotropin and cortisone. His improvement and relapses did not follow changes in medication uniformly, and any apparent relationship may have been coincidence rather than cause and effect. A septic process such as tuberculous meningitis could explain the headache, fever and the elevation of cell count and protein content of the cerebrospinal fluid. I do not know whether one can explain the visual changes on this basis; such changes suggest a mass lesion near the chiasm, with superimposed infection. Because the symptoms began five months before signs of an infectious process appeared, I would consider the presence of a mass lesion as more likely.

DR. BASTRON: Do you think he has two diseases?

DR. FRAZIER: It is highly possible.

DR. DAVID DALY†: It is asking a lot to expect a man to have a brain tumor and encephalitis, or a brain tumor and independent tuberculous meningitis. Therefore we ought to try to tie this all together in some fashion. A cholesteatoma at times will produce aseptic meningitis, with pleocytosis and increased protein content of the spinal fluid. Seeding of the subarachnoid space by a tuberculoma is another possibility to be considered in accounting for the entire course of one disease. The duration would seem long for the usual course of encephalitis but with present information we cannot be certain. The apparent response to Streptomycin or Corticotropin may be a fortuitous occurrence.

DR. C. H. MILLIKAN†: I wish to emphasize that in an illness like this, when there is no emergency and time is available, it is desirable to get all the information one can to avoid being misled. One would like to know the concentration of sugar and chloride in the spinal fluid, the cytologic characteristics of the spinal fluid, the results of blood agglutinations for Brucella, and the results of general laboratory tests, as well as the findings on physical and neurologic examinations.

DR. FRAZIER: I should like to inquire as to a possible causal relationship between the use of Corticotropin and the development of diabetes insipidus-like symptoms.

DR. BASTRON: Perhaps we can talk about that later. At the time of the admission of the patient here, he was noted to have a pasty complexion and rather sparse hair. His behavior was peculiar and inappropriate, and his remarks were often bizarre. His temperature was 99.4 degrees F. and his blood pressure 135 mm. of mercury systolic and

90 mm. diastolic. Visual acuity was 4/60 on the left and 2/60 on the right, and the optic disks were considered to be structurally full. The pupils reacted somewhat sluggishly to light and accommodation. The deep tendon reflexes were brisk except that the quadriceps femoris reflexes were diminished. There was a static tremor of the hands and there was slight dysmetria bilaterally.

Dr. Broadbent, would you discuss this case and then suggest what further studies and laboratory examinations might have been helpful?

DR. J. C. BROADBENT†: The diagnosis is still not clear. I would think of tuberculosis and other infections, but a tumor is still a possibility. I would like, in addition to the routine tests, a determination of the sedimentation rate and an agglutination test for Brucella. The usual acute infections would seem to be excluded by the long course of the illness.

DR. BASTRON: The specific gravity of the urine was 1.005. Urinalysis including a qualitative test for porphyrins gave negative results. The value for hemoglobin was 11.4 gm. per 100 cc., and the erythrocytes numbered 4,110,000 and the leukocytes 5,100 per cubic millimeter. The differential count was: lymphocytes 46, monocytes 4, neutrophils 45, eosinophils 4 and basophils 1. There was hypochromasia, polychromasia and basophilic stippling. The sedimentation rate was 61 mm. in one hour. The following tests and examinations gave negative or normal results: blood Kline test for syphilis; agglutination for Brucella; determination of heterophil antibodies, blood urea, fasting blood sugar and blood protein; and roentgenologic examination of the thorax and head. Two examinations of the spinal fluid made at an interval of 11 days gave similar results. The results of the first were: pressure, 12.5 cm. of water; color, slightly xanthochromic; cell count, 15 lymphocytes, 409 polymorphonuclear leukocytes, 3 erythrocytes and 4 unidentified cells per cu. mm.; protein, 1,000 mg. per 100 ml.; sugar, 47 mg. per 100 ml.; chlorides, 705 mg. per 100 ml.; Wassermann reaction, negative; culture for pyogenic organisms, negative; and the gold curve, 0001121100. The results of guinea pig inoculation, reported later, were negative.

DR. BASTRON: Dr. Rushton, does this help us any?

DR. J. G. RUSHTON‡: It confirms the fact that he still has active trouble. The predominance of polymorphonuclear leukocytes is ordinarily associated with acute inflammation but the normal concentrations of sugar and chloride suggest that it is not a bacterial infection. The value for protein is unusually high for meningitis, chronic or otherwise. The negative results of cultures and guinea pig inoculation correlate the lack of change in values for sugar and chlorides. Although the sedimentation rate was 61 mm., we have little evidence either for or against systemic infection with secondary spread ot the nervous system.

DR. BASTRON: Determination of the visual fields was attempted but cooperation was poor because of the patient's mental state. Dr. Wagener‡ felt reasonably certain that there was a cecocentral scotoma in the right eye superimposed upon incongrous left lower homonymous scotomas. These findings suggested a lesion involving the right optic nerve and tract, and possibly the left optic nerve. The electroencephalogram showed almost continuous diffuse rhythm of 4 to 6 per second, most marked in the temporal areas bilaterally and inhibited with opening of the eyes; with hyperventilation there were rhythmic bifrontal bursts of high-voltage discharge at a rate of 2½ per second. There was some superimposed delta activity which was most marked in the right frontotemporal area.

DR. BASTRON: Dr. Daly, would you comment on the report on the electroencephalogram?

DR. DALY: One would prefer to look at the actual record. However, on the basis of the report it would seem to be one of those records with considerable bilaterally synchronous dysrhythmia. In our experience such a record is often associated with a lesion around the third ventricle, a tumor of the basal ganglia, or a lesion around the path of ventricular flow, producing hydrocephalus of the third ventricle. The occurrence of some delta activity, more marked on the right side in association with the bilaterally synchronous dysrhythmia, suggests a lesion in the wall of the third ventricle with involvement of adjacent cortex. This is not the type of record we expect in diffuse inflammatory encephalitis.

In this case we seem to keep returning to consideration of the third ventricle and hypothalamic region. Isn't it correct that patients with craniopharyngiomas often have personality disturbance?

DR. L. M. EATON†: I would not know the statistical incidence of such disturbance, but I can recall patients with craniopharyngioma who had mental symptoms as the presenting complaint. In most instances, disturbances of vision are an early complaint.

DR. BASTRON: Dr. Brown, would you comment on your impressions at the time you examined this patient?

DR. BROWN: When I saw this patient his general appearance, including the yellow pasty complexion associated with fine sparse hair, resembled that seen in panpituitary insufficiency. This appearance combined with visual loss and headache of long duration directed our attention to the pituitary, chiasmal and hypothalamic region. The visual fields indicated involvement of the right optic nerve and tract and the roentgenogram of the head was normal. This combination of findings would be quite atypical of a pituitary tumor. An earlier patient of mine with similar appearance, headache, visual loss, personality change, spinal fluid pleocytosis and normal roentgenogram of the head turned out to have a craniopharyngioma. Thus alerted, craniopharyngioma seemed to us the most likely diagnosis in this instance. Despite this we felt obligated to study the patient for possible infectious causes before proceeding with surgical treatment.

DR. BASTRON: The 17-ketosteroids measured 1.2 mg. in 24 hours, which is considered low. I have asked Dr. Myers to comment on the endocrinologic aspects of this case.

DR. W. P. L. MYERS†: Not all patients with pituitary tumors have pituitary insufficiency. However, whether hypopituitarism is evident or not, preparation with cortisone should be carried out because of the possibility that the surgical procedure will result in significant pituitary injury. There is insufficient evidence for a "routine program" but it has been our usual practice to give cortisone as follows: 100 to 200 mg. intramuscularly 24 hours before operation and 100 to 200 mg. intramuscularly the day of operation. Postoperatively it is administered in steadily decreasing doses: 75 mg. the second day, 50 mg. the third day and 25 mg. the fourth day. Patients with hypopituitarism or adrenal insufficiency may show psychotic reactions if doses of cortisone much exceeding 25 mg. a day are continued for more than a few days beyond the period of stress. Needless to say, preoperative correction of any electrolyte disturbance (usually hyponatremia, hypochloremia and hyperkaliemia) should be part of any therapeutic program.

Desoxycorticosterone acetate (DCA) and adrenal cortical extract are rarely necessary except in instances of severe adrenal insufficiency.

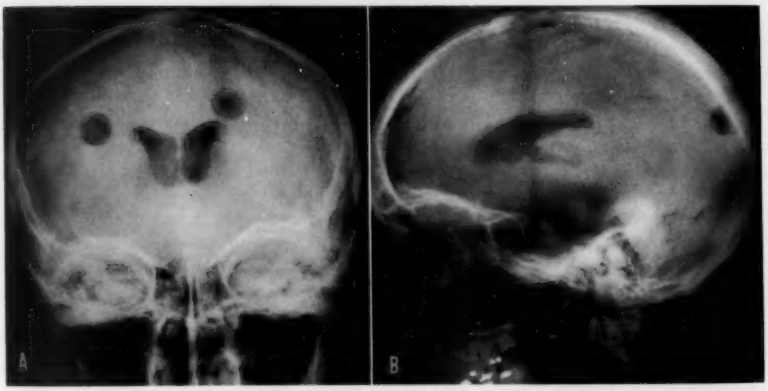

FIG. 1A and B. Ventriculograms made in the brow-up anteroposterior and right lateral projections. See text for details.

Administration of thyroid is usually unnecessary and should not be undertaken unless adrenal insufficiency has been controlled with cortisone. An adrenal crisis can be induced if this precaution is not observed.

The question has been raised as to a possible causal relationship between the use of Corticotropin in this case and the development of diabetes insipidus-like symptoms. Such symptoms (salt retention, thirst, polydipsia and polyuria) have been produced experimentally by the administration of DCA but I know of no instance of this syndrome in patients after treatment with Corticotropin. It is possible that increased metabolic breakdown products (after treatment with Corticotropin) might lead to polyuria as a result of the increased load of solute. The polyuria might then initiate thirst and polydipsia. In a patient with hypopituitarism observed by Dr. Salassa‡ in our metabolic unit, latent diabetes insipidus became apparent after cortisone therapy, indicating that adrenocortical function is apparently necessary for the full appearance of the symptoms of this disorder. It is conceivable that Corticotropin might produce such a picture by the same means but the data do not permit any such conclusion in this case.

Whether or not this patient had true diabetes insipidus remains in doubt. He apparently did not manifest the symptoms while here. Although not conclusive, the postoperative specific gravity of the urine of 1.010 (while the patient was being treated with cortisone) would not favor the diagnosis.

DR. BASTRON: During hospitalization prior to operation, covering a total period of 19 days, the patient was afebrile but had periods of confusion and disorientation. On one occasion he had a grand mal convulsion. A ventriculogram was made just prior to operation, and this will be commented upon by Dr. Holman.

DR. C. B. HOLMAN‡: Ventriculograms made in the brow-up anteroposterior and right lateral projections demonstrate a low-grade symmetrical dilation of the lateral ventricles without lateral displacement or deformity (figure 1). The superior portion of the third ventricle is filled with gas and is dilated. Its anterior and inferior portions are not well demonstrated. This ventricle appears to have been displaced superiorly by a mass near

the midline in the suprasellar region. This distortion of the third ventricle probably accounts for the ventricular dilation demonstrated.

Ventriculograms made in the browdown projections show filling of the suprapineal recess, although there is no gas in the aqueduct or fourth ventricle.

DR. BASTRON: The operative and pathologic findings will be described by Dr. Kernohan.

DR. J. W. KERNOHAN‡: The region of the sella turcica was explored and a tumor was found between the optic chiasm and the pituitary gland. The tumor was visible both anterior and posterior to the optic chiasm and had invaded the floor of the third ventricle. The right optic nerve and chiasm were pushed forward and upward by the tumor, and the optic chiasm was displaced slightly to the right. The right optic nerve and chiasm were stretched and compressed, and at the point where the right anterior cerebral artery crossed the optic chiasm and right optic nerve there was a notch or groove made by the pulsating artery. Subtotal removal of the tumor was done. Some portions were not removed because of their inaccessibility.

On histologic examination the tumor proved to be an adamantinoma. In most respects it was fairly typical, with squamous and basal types of cells, and the basal cells rested on the characteristically vascular mesenchymal stroma. This tumor had several unusual features. There was little cornification and no calcification in any of the sections. One very unusual feature was the large number of polymorphonuclear leukocytes in both the epithelial and stromal portions. There was no obvious explanation for these polymorphonuclear leukocytes since the tumor was neither infected nor necrotic.

In spite of these unusual features I would consider this a fairly characteristic adamantinomatous type of craniopharyngioma.

DR. BASTRON: Immediately following operation, the patient's temperature rose to 106 degrees F. but then fell sharply to normal. During the next six days it fluctuated between 98 degrees and 102 degrees F.; after that it was normal. He continued to have periods of confusion. During the first five days he received 50 to 100 mg. of cortisone twice a day in decreasing doses. He was dismissed to go home 15 days postoperatively. A letter received from his wife two and a half months later and three months postoperatively stated that he had not been able to return to work and that he continued to have periods of confusion. He was taking little interest in his family.

The *earliest* symptoms of encephalitis and of tuberculous hydrocephalus are, then, those which relate to the *cerebral* functions, which are *exalted*. These functions are so slightly developed in infants, that their state of exaltation too frequently passes unnoticed. Yet the phenomena are obvious enough, if there be but a careful observation on the part of the parent or nurse, on whom the duty of noticing the *dawn* of these diseases must devolve.

—Marshall Hall in *Lectures on the Nervous System and Its Diseases*, published in 1876.

PAGES 543-544 MISSING, COVER PAGES FOR INDEX.

INDEX OF AUTHORS

Alexander, Leo (co-author), Role of Food Allergy in Multiple Sclerosis, 412.
Alpers, Bernard J. (co-author), Subarachnoid Hemorrhage as a Cause of Sudden Death, 203.

Bailey, Orville T. (co-author), Clinical Pathologic Conference, 263.
Baker, A. B., Progress and Problems in American Neurology, 73. Rehabilitation of the Neurologically Disabled Child, 441.
Barcroft, Henry (co-author), Action of Adrenalin and Noradrenalin on the Tremor in Parkinson's Disease, 154.
Barris, Ralph W., Use of Benadryl for Symptomatic Relief of "Thalamic Pain," 59. (co-author), Vertebral Artery Aneurysm, 356. (co-author), Effects of Cortisone in Myotonia Atrophica, 496.
Bastron, James A. (co-author), Clinical Pathologic Conference, 537.
Bayless, Allan E. (co-author), Stellate Block: Technique, Dangers and Safeguards, 529.
Bender, Morris B. (co-author), The Face-Hand Test as a Diagnostic Sign of Organic Mental Syndrome, 46. (co-author), Extinction of Taste Sensation on Double Simultaneous Stimulation, 195.
Boshes, Benjamin (co-author), Sensory Return in Partial and Recovery Spinal Cord Lesions, 81.
Boswell, Wade H. (co-author), Comparison of Provocative Agents in the Epilepsies and in Controls, 481.
Brodal, Alf, The Role of Neuroanatomy in Neurologic Research, 207.
Brodrick, R. J. (co-author), The Hematologic, Gastric Acidity and Cerebrospinal Fluid Findings in Multiple Sclerosis, 514.
Brown, Joe R., Management of Patients with Brain Damage, 273. (co-author), Clinical Pathologic Conference, 537.
Brown, Meyer (co-author), Sensory Return in Partial and Recovery Spinal Cord Lesions, 81.
Burch, N. (co-author), Clinical Pathologic Conference, 446.
Bushard, Marcus (co-author), Vertebral Artery Aneurysm, 356.

Cameron, Richard R. (co-author), Hypnosis in Differentiation of Epileptic from Convulsive-like Seizures, 395.
Cohn, Robert, On Certain Aspects of the Sensory Organization of the Human Brain, III. A Patterned Response to Three Simultaneously Applied Cutaneous Stimuli, 140. (co-author), Comparison of Provocative Agents in the Epilepsies and in Controls, 481.
Constable, Kate (co-author), Preliminary Study of a New Antiparkinson Agent, 233.
Cooper, Irving S. (co-author), Metabolic Disorders in Paraplegics, 332.
Crouch, Richard L. (co-author), Sensory Return in Partial and Recovery Spinal Cord Lesions, 81.
Cull, Virginia L. (co-author), Clinical Pathologic Conference, 446.

Daniels, Luman E., Obituary of Harold Robert Carter, 169.
Darnley, J. Dana, Chloromycetin and Streptomycin in the Treatment of Meningitis due to B. Proteus, 69.
Dekaban, A. S. (co-author), The Hematologic, Gastric Acidity and Cerebrospinal Fluid Findings in Multiple Sclerosis, 514.
DeJong, Russell N. (co-author), Clinical Pathologic Conference, 350. To Our Readers and Authors, 457. (co-author), Treatment of Headache with Ergotamine-Caffeine Suppositories, 477.
Dickerson, Willard W. (co-author), Electroencephalographic Study of Patients with Tuberous Sclerosis, 248.
Dimitrijevic, D. T., Lasègue Sign, 453.
Doshay, Lewis J. (co-author), Preliminary Study of a New Antiparkinson Agent, 233.

Ehrentheil, Otto F. (co-author), Role of Food Allergy in Multiple Sclerosis, 412.
Ekbom, K. A. (co-author), Perioral Reflexes, 103.

Faulconer, Albert, Jr. (co-author), A New Curare Antagonist in Electroshock Therapy, 226.
Feldman, Daniel S. (co-author), Extinction of Taste Sensation on Double Simultaneous Stimulation, 195. (co-author), Double Simultaneuos Stimulation Phenomena in Spinal Cord Disease, 509.
Fields, William S. (co-author), Relief of Pain in Trigeminal Neuralgia by Crystalline Vitamin B_{12}, 131.
Fink, Max (co-author), The Face-Hand Test as a Diagnostic Sign of Organic Mental Syndrome, 46.
Flicker, David J., Trauma in Multiple Sclerosis, 520.
Foltz, Eldon L. (co-author), Serial Electroencephalography in Vascular Lesions of the Brain, 311.
Foster, J. J. (co-author), Clinical Pathologic Conference, 65.
French, John D. (co-author), Stellate Block: Technique, Dangers and Safeguards, 529.
Friedlander, Walter J., Alterations of Basal Ganglion Tremor during Sleep, 222.

Fromer, Stephen (co-author), Preliminary Study of a New Antiparkinson Agent, 233.

Gitt, Joseph J. (co-author), Subacute Encephalitis—Three Year Survival with Long-term Remission, 488.
Gonda, V. E. (co-author), Clinical Pathologic Conference, 446.
Green, Martin (co-author), The Face-Hand Test as a Diagnostic Sign of Organic Mental Syndrome, 46.
Heimburger, Robert E. (co-author), Clinical Pathologic Conference, 263.
Hellman, C. David (co-author), Electroencephalographic Study of Patients with Tuberous Sclerosis, 248.
Hoedemaker, Edward D. (co-author), Psychologic Tests in the Diagnosis of Organic Brain Disease, 144.
Hoen, Thomas I. (co-author), Metabolic Disorders in Paraplegics, 332.
Hoff, Hebbel E. (co-author), Relief of Pain in Trigeminal Neuralgia by Crystalline Vitamin B_{12}, 131.
Hofmann, William W., The Syndrome of Periodic Paralysis, 1.
Hunter, John (co-author), Behavior Deficits following Diencephalic Lesions, 112.

Jernelius, B. (co-author), Perioral Reflexes, 103.

Karnosh, L. J. (co-author), Modification of Signs in Multiple Sclerosis with Tetraethylammonium Chloride, 525.
Kelly, Michael, Spread of Sensory and Motor Loss after Nerve Injury, 36.
Krueger, Erich G. (co-author), Oligodendrogliomas Arising from Structures of the Posterior Fossa, 461.
Krupp, George (co-author), Oligodendrogliomas Arising from Structures of the Posterior Fossa, 461.
Kugelberg, E. (co-author), Perioral Reflexes, 103.

Lambert, Edward H. (co-author), A New Curare Antagonist in Electroshock Therapy, 226.
Lanchner, Abraham J., Headache in Ophthalmic Practice, 471.
Landau, William M., The Essential Mechanism in Myotonia—An Electromyographic Study, 369. (co-author), Subacute Encephalitis—Three Year Survival with Long-term Remission, 488.
Loscalzo, Anthony E., Mesantoin in the Control of Epilepsy, 403.

Mackay, Roland P., Obituary, George Boris Hassin, 455.
Magee, Kenneth R. (co-author), Treatment of Headache with Ergotamine-Caffeine Suppositories, 477.
Malamud, N. (co-author), Clinical Pathologic Conference, 446.
McIntyre, Aurelia P. (co-author), Neuromyelitis Optica with Xanthochromia and Spinal Block, 96.
McIntyre, Howard D. (co-author), Neuromyelitis Optica with Xanthochromia and Spinal Block, 96.
Merritt, H. Houston (co-author), Clinical Pathologic Conference, 161.
Meyer, John S. (co-author), Behavior Deficits following Diencephalic Lesions, 112.
Michelsen, Jost J., Neurologic Manifestations following Spinal Anesthesia, 255.
Murray, M. E. Miriam (co-author), Psychologic Tests in the Diagnosis of Organic Brain Disease, 144.

Nardini, John E. (co-author), Comparison of Provocative Agents in the Epilepsies and in Controls, 481.
Nielsen, J. M. (co-author), Clinical Pathologic Conference, 65.

Peterson, Donald B. (co-author), Hypnosis in Differentiation of Epileptic from Convulsive-like Seizures, 395.
Peterson, Elizabeth (co-author), Action of Adrenalin and Noradrenalin on the Tremor in Parkinson's Disease, 154.

Rome, Howard P. (co-author), A New Curare Antagonist in Electroshock Therapy, 226.
Roseman, E. (co-author), Serial Electroencephalography in Vascular Lesions of the Brain, 311.
Rosen, Samuel, Effect of Stimulation and Section of the Chorda Tympani Nerve, 244.
Ross, Alexander T. (co-author), Clinical Pathologic Conference, 263.
Rozanski, J., Peduncular Hallucinosis following Vertebral Angiography, 341.

Scharenberg, Konstantin (co-author), Clinical Pathologic Conference, 350.
Scheinker, I. Mark, Clinical Significance, Histopathology and Classification of Cerebral Swelling, 177.
Schmidt, Richard P. (co-author), Serial Electroencephalography in Vascular Lesions of the Brain, 311.
Schulman, Maurice H. (co-author), Role of Food Allergy in Multiple Sclerosis, 412.
Schwab, Robert S. (co-author), Action of Adrenalin and Noradrenalin on the Tremor in Parkinson's Disease, 154.

Sciarra, Daniel (co-author), Korsakoff's Psychosis Associated with Cerebral Tumors, 427.
Shapiro, Mortimer F. (co-author), Double Simultaneous Stimulation Phenomena in Spinal Cord Disease, 509.
Silverstein, Alexander, Significance of Cerebral Fat Embolism, 292.
Sprofkin, Bertram E. (co-author), Korsakoff's Psychosis Associated with Cerebral Tumors, 427.
Steegmann, A. Theodore, Syndrome of the Anterior Spinal Artery, 15.
Stein, Joseph M., Cerebral Angiography in Diagnosis of Subdural Hematoma, 389.
Steiner, Gabriel, Environmental Studies in Multiple Sclerosis, 260.
Stevenson, Lewis D., Obituary, R. Foster Kennedy, 360.
Strassman, Harvey D. (co-author), Effects of Cortisone in Myotonia Atrophica, 496.
Sumner, John W., Jr. (co-author), Hypnosis in Differentiation of Epileptic from Convulsive-like Seizures, 395.

Timme, Arthur R., What Has Neurology to Offer Child Guidance?, 435.
Trowbridge, William V. (co-author), Stellate Block: Technique, Dangers and Safeguards, 529.
Tucker, Howard J. (co-author), Modification of Signs in Multiple Sclerosis with Tetraethylammonium Chloride, 525.
Tucker, Weir M. (co-author), Subarachnoid Hemorrhage as a Cause of Sudden Death, 203.

Waugh, T. R. (co-author), The Hematologic, Gastric Acidity and Cerebrospinal Fluid Findings in Multiple Sclerosis, 514.
Westerberg, Martha R. (co-author), Treatment of Headache with Ergotamine-Caffeine Suppositories, 477.
Williams, Guy H., Jr. (co-author), Modification of Signs in Multiple Sclerosis with Tetraethylammonium Chloride, 525.
Winkelman, N. W., Neurologic Symptoms following Accidental Intraspinal Detergent Injection, 284.
Wolf, Abner (co-author), Clinical Pathologic Conference, 161.
Worthington, R. V. (co-author), Clinical Pathologic Conference, 446.

Yuhl, Eric (co-author), Vertebral Artery Aneurysm, 356.

Ziegler, Dewey K., Extinction Phenomenon in Patients with Verified Cerebral Tumors, 501.

SUBJECT INDEX

Accidental intraspinal detergent injection, neurologic symptoms following, 284.
Action of Adrenalin and Noradrenalin on the tremor in Parkinson's disease, 154.
Adrenalin, action of, in Parkinson's disease, 154.
Allergy, role of food, in multiple sclerosis, 412.
Alterations of basal ganglion tremor during sleep, 222.
American Academy of Neurology, program of 1953 meeting, 170.
Anesthesia, spinal, neurologic manifestations following, 255.
Aneurysm, vertebral artery, 356.
Angiography,
  cerebral, in diagnosis of subdural hematoma, 389.
  vertebral, hallucinosis following, 341.
Anterior spinal artery, syndrome of, 15.
Antiparkinson agent, new, preliminary study of, 233.

B_{12}, vitamin, relief of pain in trigeminal neuralgia by, 131.
Basal ganglion tremor, alterations of, during sleep, 222.
Behavior deficits following diencephalic lesions, 112.
Benadryl, use of, for symptomatic relief of thalamic pain, 59.
Block, spinal, neuromyelitis optica with, 96.
Book reviews:
  Atlas of Cross Section Anatomy of the Brain, A. T. Rasmussen, 80.
  Brain Tumors of Childhood, Henry M. Cuneo and Carl W. Rand, 271.
  Causalgia, Frank H. Mayfield, 176.
  Current Therapy—1952, Howard F. Conn, 368.
  Diagnosis of Nervous Diseases, James Purves-Stewart and C. Worster-Drought, 459.
  Diseases of the Nervous System, W. Russell Brain, 175.
  Epileptic Seizure Patterns, Wilder Penfield and Kristian Kristiansen, 79.
  Frontal Lobotomy and Affective Behavior, John F. Fulton, 78.
  History of Neurological Surgery, A. Earl Walker, 363.
  Introduction to Neuropathology, Samuel H. Hicks and Shields Warren, 80.

Medical Neuropathology, I, Mark Scheinker, 77.
Modern Headache Therapy, Arnold P. Friedman, 272.
Modern Trends in Neurology, Anthony Feiling, 172.
Neurosurgery—An Historical Sketch, Gilbert Horrax, 364.
Normal Cerebral Angiogram, Arthur Ecker, 364.
Precepts and Counsels on Scientific Investigation, S. Ramon y Cajal, 366.
Problems in Cerebellar Physiology, G. Moruzzi, 175.
Skull Fractures and Brain Injuries, Harry E. Mock, 460.
Studies in Lobotomy, Milton Greenblatt, Robert Arnot and Harry C. Solomon, 173.
Surgery of the Peripheral Nerves, Emil Seletz, 460.
Textbook of Clinical Neurology, J. M. Nielsen, 78.
Textbook of Orthopedics, M. Beckett Howorth, 365.
Thalamus of the Macaca Mulatta — An Atlas for Use with the Stereotaxic Instrument, Jerzy Olszewski, 366.

Brain,
damage, management of patients with, 273.
disease, organic, psychologic tests in diagnosis of, 144.
human, on certain aspects of the sensory organization of, 140.
serial EEG in vascular lesions of, 311.

Carter, Harold Robert, obituary, 169.
Case reports:
Chloromycetin and Streptomycin in treatment of meningitis due to B. proteus, 69.
Vertebral artery aneurysm, 356.
Cerebral angiography in diagnosis of subdural hematoma, 389.
Cerebral fat embolism, significance of, 292.
Cerebral swelling, clinical significance, histopathology and classification of, 177.
Cerebral tumors,
extinction phenomenon in patients with, 501.
Korsakoff's psychosis associated with, 427.
Cerebrospinal fluid findings in multiple sclerosis, 514.
Child guidance, what has neurology to offer, 435.
Child, rehabilitation of the neurologically disabled, 441.
Chloromycetin and Streptomycin in treatment of meningitis due to B. proteus, 69.
Chorda tympani nerve, effect of stimulation and section of, 244.
Classification of cerebral swelling, 177.
Clinical pathologic conferences, 65, 161, 263, 350, 446, 537.
Clinical significance, histopathology and classification of cerebral swelling, 177.
Comparison of provocative agents in the epilepsies and in controls, 481.
Cord, spinal, lesions, sensory return in, 81.
Cortisone, effects of, in myotonia atrophica, 496.
Curare antagonist, new, in electroshock therapy, 226.
Cutaneous stimuli, response to three simultaneously applied, 140.

Death, sudden, subarachnoid hemorrhage as cause of, 203.
Detergent injection, accidental intraspinal, neurologic symptoms following, 284.
Deficits, behavior, following diencephalic lesions, 112.
Diagnosis of
organic brain disease, psychologic tests in, 144.
subdural hematoma, cerebral angiography in, 389.
Diagnostic sign, face-hand test as, 46.
Diencephalic lesions, behavior deficits following, 112.
Double simultaneous stimulation phenomena in spinal cord disease, 509.

Editorials:
Progress and Problems in American Neurology, 73.
To our readers and authors, 457.
Effect of stimulation and section of the chorda tympani nerve, 244.
Effects of cortisone in myotonia atrophica, 496.
Electroencephalographic study of patients with tuberous sclerosis, 248.
Electroencephalography, serial, in vascular lesions of the brain, 311.
Electromyographic study — essential mechanism in myotonia, 369.
Electroshock therapy, new curare antagonist in, 226.
Embolism, significance of cerebral fat, 292.
Encephalitis, subacute, 488.
Environmental studies in multiple sclerosis, 260.
Epilepsies, comparison of provocative agents in, 481.
Epilepsy, Mesantoin in the control of, 403.
Epileptic seizures, hypnosis in differentiation of, 395.
Ergotamine-caffeine suppositories, treatment of headache with, 477.
Essential mechanism in myotonia—electromyographic study, 369.

Extinction
of taste sensation on double simultaneous stimulation, 195.
phenomenon in patients with verified cerebral tumors, 501.

Face-hand test as a diagnostic sign of organic mental syndrome, 46.

Gastric acidity findings in multiple sclerosis, 514.

Hallucinosis, peduncular, following vertebral angiography, 341.
Hand, face-, test as a diagnostic sign of organic mental syndrome, 46.
Hassin, George Boris, obituary, 455.
Headache
in ophthalmic practice, 471.
treatment of, with ergotamine-caffeine suppositories, 477.
Hematologic, gastric acidity and cerebrospinal fluid findings in multiple sclerosis, 514.
Hematoma, subdural, diagnosis of, 389.
Hemorrhage, subarachnoid, as a cause of sudden death, 203.
Histopathology, clinical significance, and classification of cerebral swelling, 177.
Historical note: Lasègue sign, 453.
Hypnosis in differentiation of epileptic from convulsive-like seizures, 395.

Injury, nerve, spread of sensory and motor loss after, 36.
Intraspinal, accidental detergent injection, 284.

Kennedy, R. Foster, obituary, 360.
Korsakoff's psychosis associated with cerebral tumors, 427.

Lasègue sign, 453.
Lesions,
diencephalic, behavior deficits following, 112.
of brain, vascular, EEG in, 311.
spinal cord, sensory return in, 81.

Management of patients with brain damage, 273.
Meningitis, Chloromycetin and Streptomycin in treatment of, 69.
Mental syndrome, organic, face-hand test as a diagnostic sign of, 46.
Mesantoin in the control of epilepsy, 403.
Metabolic disorders in paraplegics, 332.
Modification of signs in multiple sclerosis with tetraethylammonium chloride, 525.
Motor loss, spread of sensory and, after nerve injury, 36.
Multiple sclerosis,
environmental studies in, 260.
hematologic, gastric acidity and cerebrospinal fluid findings in, 514.
modification of signs in, with tetraethylammonium chloride, 525.
role of food allergy in, 412.
trauma in, 520.
Myotonia atrophica, effects of cortisone in, 496.
Myotonia, essential mechanism in, 369.

Nerve injury, spread of sensory and motor loss after, 36.
Neuralgia, trigeminal, relief of pain in, 131.
Neuroanatomy, role of, in neurologic research, 207.
Neurologic manifestations following spinal anesthesia, 255.
Neurologic symptoms following accidental intraspinal detergent injection, 284.
Neurologically disabled child, rehabilitation of, 441.
Neurology, American, progress and problems in (editorial), 73.
Neurology, what has, to offer child guidance, 435.
Neuromyelitis optica with xanthochromia and spinal block, 96.
New curare antagonist in electroshock therapy, 226.
Noradrenalin, action of, in Parkinson's disease, 154.

Obituaries:
Harold Robert Carter, 169.
George Boris Hassin, 455.
R. Foster Kennedy, 360.
Oligodendrogliomas arising from structures of the posterior fossa, 461.
On certain aspects of the sensory organization of the human brain. III. A patterned response to three simultaneously applied cutaneous stimuli, 140.
Ophthalmic practice, headache in, 471.
Optica, neuromyelitis, with xanthochromia and spinal block, 96.
Organic mental syndrome, face-hand test as a diagnostic sign of, 46.

Pain,
relief of, in trigeminal neuralgia, 131.
thalamic, use of Benadryl for symptomatic relief of, 59.
Paralysis, periodic, syndrome of, 1.
Paraplegics, metabolic disorders in, 332.
Parkinson, anti-, agent, preliminary study of, 233.
Parkinson's disease, action of Adrenalin and Noradrenalin on the tremor in, 154.
Peduncular hallucinosis following vertebral angiography, 341.
Periodic paralysis, syndrome of, 1.
Perioral reflexes, 103.

Posterior fossa, oligodendrogliomas arising from structures of, 461.
Preliminary study of a new antiparkinson agent, 233.
Progress and problems in American neurology (editorial), 73.
Proteus, B., Chloromycetin and Streptomycin in treatment of meningitis due to, 69.
Provocative agents in the epilepsies, comparison of, 481.
Psychologic tests in the diagnosis of organic brain disease, 144.
Psychosis, Korsakoff's, associated with cerebral tumors, 427.

Reflexes, perioral, 103.
Rehabilitation of the neurologically disabled child, 441.
Relief of pain in trigeminal neuralgia by crystalline vitamin B_{12}, 131.
Relief, symptomatic, of thalamic pain, use of Benadryl for, 59.
Response, patterned, to simultaneously applied cutaneous stimuli, 140.
Role of
  food allergy in multiple sclerosis, 412.
  neuroanatomy in neurologic research, 207.

Seizures, hypnosis in differentiation of, 395.
Sensation, taste, extinction of, 195.
Sensory and motor loss, spread of, after nerve injury, 36.
Sensory organization of the human brain, certain aspects of, 140.
Sensory return in partial and recovery spinal cord lesions, 81.
Serial electroencephalography in vascular lesions of the brain, 311.
Sign,
  diagnostic, face-hand test as, 46.
  Lasègue, 453.
  Significance of cerebral fat embolism, 292.
Signs, modification of, in multiple sclerosis, 525.
Sleep, alterations of basal ganglion tremor during, 222.
Spinal anesthesia, neurologic manifestations following, 255.
Spinal artery, anterior, syndrome of, 15.
Spinal block, neuromyelitis optica with, 96.
Spinal cord disease, double simultaneous stimulation phenomena in, 509.
Spinal cord lesions, sensory return in partial and recovery, 81.
Spread of sensory and motor loss after nerve injury, 36.
Stellate block: technique, dangers and safeguards, 529.
Stimulation and section of chorda tympani, effect of, 244.
Stimulation, double simultaneous,
  extinction of taste sensation on, 195.
  in spinal cord disease, 509.
Streptomycin, Chloromycetin and, in treatment of meningitis due to B. proteus, 69.
Subacute encephalitis—three year survival with long-term remission, 488.
Subarachnoid hemorrhage as a cause of sudden death, 203.
Subdural hematoma, diagnosis of, 389.
Syndrome of
  periodic paralysis, 1.
  the anterior spinal artery, 15.

Taste sensation, extinction of, 195.
Test, face-hand, as a diagnostic sign of organic mental syndrome, 46.
Tests, psychologic, in diagnosis of organic brain disease, 144.
Tetraethylammonium chloride, modification of signs in multiple sclerosis with, 525.
Thalamic pain, use of Benadryl for symptomatic relief of, 59.
Therapy, electroshock, new curare antagonist in, 226.
To our readers and authors (editorial), 457.
Trauma in multiple sclerosis, 520.
Treatment of
  headache with ergotamine-caffeine suppositories, 477.
  meningitis, Chloromycetin and Streptomycin in, 69.
Treatment reviews:
  Rehabilitation of the neurologically disabled child, 441.
  Stellate Block: Technique, Dangers and Safeguards, 529.
Tremor, alterations of basal ganglion, during sleep, 222.
Tremor in Parkinson's disease, action of Adrenalin and Noradrenalin on, 154.
Trigeminal neuralgia, relief of pain in, by crystalline vitamin B_{12}, 131.
Tuberous sclerosis, EEG study of, 248.
Tumors, cerebral,
  extinction phenomenon in patients with, 501.
  Korsakoff's psychosis associated with, 427.

Use of Benadryl for symptomatic relief of thalamic pain, 59.

Vascular lesions of brain, serial EEG in, 311.
Vertebral angiography, hallucinosis following, 341.
Vertebral artery aneurysm, 356.
Vitamin B_{12}, crystalline, relief of pain in trigeminal neuralgia by, 131.

What has neurology to offer child guidance?, 435.

Xanthochromia, neuromyelitis optica with, 96.